

THE UNIVERSITY OF ALBERTA
STEREOCHEMICAL STUDIES OF 3-METHYL ANALOGUES
OF PETHIDINE

by

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

FACULTY OF PHARMACY
AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA
(SPRING), (1969)

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

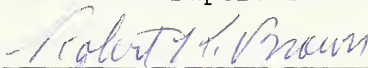
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and recommend to the Faculty of Graduate Studies for
acceptance, a thesis entitled "Stereochemical Studies
of 3-Methyl Analogues of Pethidine", submitted by
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ACKNOWLEDGEMENTS

The author wishes to express his hearty thanks and appreciation to Dr. A.F. Casy and Dr. L.G. Chatten for their able supervision, useful suggestions and constructive criticisms throughout the course of these investigations and who by their approval and disapproval of his views at various times, pointed out to him the right road to follow.

A special thanks is extended to Dr. E.L. May, Chief of the Medicinal Chemistry section of the National Institute of Health, Bethesda, Maryland, who kindly arranged the determination of the analgesic activities of the compounds synthesized during the course of these investigations. To Dr. R.T. Coutts, the author is indebted for many useful discussions.

The author gratefully acknowledges the technical assistance of Mrs. Sining Li and Mr. Willard Dylke for determining the infrared and PMR spectra and element analyses needed for this project.

The cooperation of Miss Valerie McLeod for typing the complete manuscript and Dr. (Mrs.) Gita Mukherjee who assisted greatly in proof-reading is gratefully acknowledged.

It is a pleasure to thank Dean M.J. Huston for providing necessary chemicals, financial assistance and excellent laboratory facilities.

"Nature undoubtedly, carries out her reactions on a three dimensional basis. Since drugs assist or interfere with such reactions it is important to give increasing attention to a three dimensional approach in an attempt to reduce the empiricism involved in the preparation of agents with a desired biological effect."¹⁰

A. H. Beckett (1959) .

ABSTRACT

Stereochemical studies of 4-phenylpiperidine analgesics are reviewed and attention is drawn to the importance of configuration and conformation of the molecule in producing an analgesic response.

The synthesis of 3-methyl analogues of pethidine and its related 4-propionyl derivatives forms the main project of this thesis and has been carried out by routes based on the condensation of phenylacetonitrile with various derivatives of N-2-hydroxyethyl-N-2-hydroxypropylamine. Isomeric forms of intermediate 4-cyanopiperidines have been separated and their configurations established by PMR data and by chemical correlations. Amides and amidines are separated as byproducts in these condensation reactions. Alternative routes to the pethidine analogues based upon the quasi Favorskii rearrangement of N-methyl-4-chloro-4-piperidinophenyl ketone and upon the Beckmann rearrangement of N-methyl-4-phenyl-4-piperidinophenyl ketone have been investigated.

The PMR characteristics of many of the compounds synthesized in this work are reported and provide evidence of the preferred conformation of 4-phenylpiperidine derivatives in water and other solvents and for the occurrence of protonated epimers.

Pharmacological results (hot-plate activities in mice) provide further results demonstrating the super-

iority of cis (3-Me/4-Ph) geometry over the trans arrangement in 4-phenylpiperidine analgesics and the influence of a 3-methyl substituent upon the analgesic action of this class of analgesic is discussed.

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INTRODUCTION

INTRODUCTION

On the basis of our present knowledge, it seems valid to assume that analgesia results from the interaction of a drug with a specific analgesic receptor located somewhere in the central nervous system. This receptor may be considered as a frame-work of biochemical substances such as a highly selective sequence of amino-acids, lipoproteins, phospholipid or lipid structures, which could provide an area of atoms having a chemical configuration complementary to that of the analgesic drug. The property of many enzymes to attack one of a pair of stereoisomers selectively has been known for years. The penetration of certain membranes also has been shown to be stereochemically dependent and the uptake of enantiomorphs upon naturally occurring ring surfaces is known to be selective (Beckett 1959). It is therefore, not surprising that there are many examples of stereoisomeric drug molecules which exhibit large differences in biological effects. The remarkable difference in analgesic potency exhibited by the stereoisomers of many drugs strongly suggests that a precise stereochemical arrangement of atoms in the molecule is essential, in order to produce analgesic action.

Marked differences in analgesic potency have been reported between

a) Diastereoisomers

b) Enantiomers

and a few examples are given below.

DIASTEREOISOMERS

In the 5,9-dialkyl-6,7-benzomorphans, (1), the β - isomers (in which 5,9-dialkyl groups are trans with respect to the hydroaromatic ring) are from 5 to 70 times more potent than their corresponding α -isomers, (in which 5,9-dialkyl groups are cis oriented) (Eddy and May 1966). Some detailed results are given in Table I. Here the test employed to assess analgesia is the Hot-Plate Assay (Eddy 1953) with mice as the test animal (this test is one of the most common procedures used to measure analgesic potencies relative to a standard drug such as morphine or pethidine and provides a reliable guide to the analgesic properties of a particular drug in man) .

Marked differences between the activities of diastereoisomeric reversed esters of pethidine have also been noted (Casy 1968 and references there cited). These compounds which owe their asymmetry to one or more alkyl substituents in the piperidine ring are discussed later.

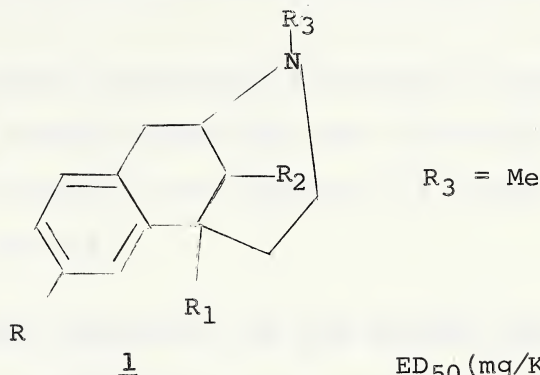
ENANTIOMORPHS:

Many asymmetric analgesics have been resolved and both enantiomorphs tested. In most cases, one

TABLE I. ANALGESIC ACTIVITIES OF RACEMIC 5,9-DIALKYL-2

(N)-METHYL-6,7-BENZOMORPHAN DIASTEREOMERS IN MICE

(Eddy and May 1966 and references cited therein)



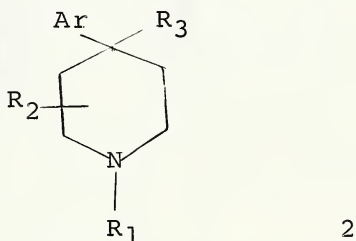
<u>No</u>	<u>R</u>	<u>R₁</u>	<u>R₂</u>	<u>Salt</u>	<u>Isomer</u>	<u>ED₅₀ (mg/Kg.)</u>	
						<u>Oral</u>	<u>Subcutaneously</u>
1.	H	Me	Me	HCl	α -	27.3	-
	H	Me	Me	HBr	β -	8.9	37.1
2.	OH	Me	Me	HCl	α -	3.0	23.9
	OH	Me	Me	HCl	β -	0.44	8.2
3.	OH	Et	Me	HCl	α -	4.9	31.7
	OH	Et	Me	HCl	β -	0.07	1.1
4.	OH	Et	Et	HCl	α -	4.2	inactive
	OH	Et	Et	HCl	β -	0.28	6.5
5.	OH	Pr	Pr	HCl	α -	71.2	-
	OH	Pr	Pr	HCl	β -	0.87	-
6.	OH	Me	Et	HCl	α -	1.5	14.8
	OH	Me	Et	HCl	β -	0.47	17.2
7.	H	Et	Et	HCl	α -	5.0	36.7
	H	Et	Et	HBr	β -	4.2	38.7

encounters a pair of enantiomers one of which has a pronounced analgesic action while the other has very little or none. A few examples are given below (see Table II).

In this thesis, attention is directed to analgesics based on 4-phenylpiperidine and a brief review of this class follows in which emphasis is placed upon stereochemical factors.

4-PHENYLPYPERIDINE ANALGESICS AND THE RELATED COMPOUNDS:

The 4-phenylpiperidine type of analgesic is historically the oldest synthetic group (pethidine was introduced clinically in 1939). The structure of this class of compound may be summarized by the general formula (2)



where R_1 may be methyl and related alkyl or arylalkyl groups, R_2 may be H, Me, Et, $-\text{CH}_2-\text{CH}=\text{CH}_2$, etc. (principally in the 3-position), Ar may be a phenyl group with a variety of substituents or related isosteric groups such as 2-furyl, 2-thienyl, etc., and R_3 may be an oxygen function including carbalkoxy, acyloxy, alkyl ketone, alkyl ether groups, etc. Some related 5- and 7-

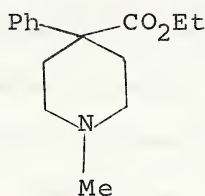
TABLE II. COMPARATIVE ANALGESIC ACTIVITIES OF ENANTIOMORPHIC PAIRS

(Mellelt and Woods 1963 and references cited therein)

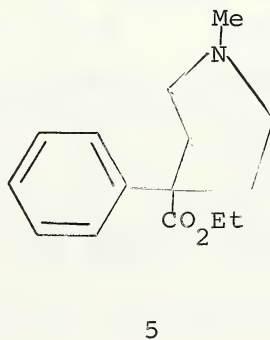
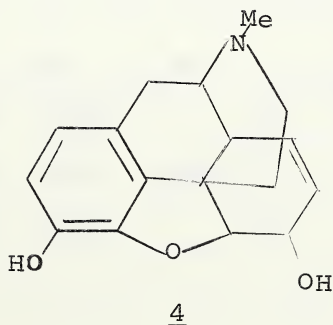
<u>No</u>	<u>Class</u>	<u>Compound</u>	<u>Enantiomer</u>	<u>ED₅₀ (mg./Kg.)</u>
				<u>Subcutaneously</u> <u>in mice</u>
1	Morphine	see p. 6	(-)	2.1
			(+)	inactive
2	Morphinan	3-Hydroxy-N-methyl-morphinan	(-)	0.5
			(+)	58.2
3	Benzomorphan	α -2-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan. HBr	(-)	1.69
			(+)	25.0
4	Methadone	Me ₂ NCH(CH ₃)CH ₂ CPh ₂ COEt	(-)	0.8
			(+)	25.7

membered derivatives also possess analgesic action.

The best known example of this class is pethidine (3) which is also known by a variety of other names such as meperidine, demerol, dolantin, isonipecaine, etc.



(The Merck Index 1960). Pethidine is a synthetic analgesic introduced by Eisleb and Schaumann in 1939. Their objective in making pethidine was to produce an antispasmodic drug with atropine-like properties. That the drug had morphine-like properties as well was a fortuitous and most unexpected discovery (the first clue was the ability of the drug to produce the Straub tail effect in rats). Only after morphine-like properties were noted in routine screening was a resemblance to part of the morphine molecule (4) assigned to the pethidine structure (5) (Eisleb and Schaumann 1939 and Schaumann 1949). These workers recognized that the 4-phenylpiperidine moiety was common to both molecules.



In view of the excellent clinical acceptance of pethidine, research in this field has expanded extensively since its original discovery. A large number of compounds related to the pethidine structure have been synthesized and screened for analgesic action. Some of them show much greater potency than pethidine (Janssen 1959, 1960). Several reviews pertaining to the chemistry and pharmacology of pethidine and related compounds have appeared during the past few years (Bergel and Morrison 1948; Braenden, et. al. 1954, 1955, 1956 and 1957; May 1960; Beckett and Casy 1962; and Mellett and Woods 1963).

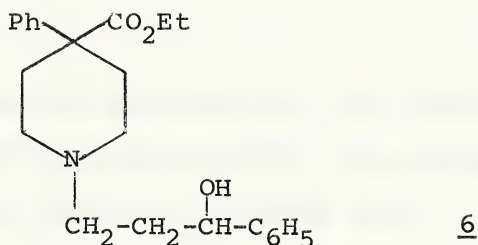
In general, analgesic properties are retained although to a reduced degree, in seven membered analogues of active piperidine derivatives but are absent or weak in five-membered congeners (see Table III).

TABLE III. ANALGESIC ACTIVITIES OF SOME AZABICYCLOALKANE DERIVATIVES (Beckett and Casy 1961 and references cited therein)

$ \begin{array}{c} \text{R} - \text{N} \begin{array}{l} \nearrow (\text{CH}_2)_x \\ \searrow (\text{CH}_2)_y \end{array} \text{C} \begin{array}{l} \nearrow \text{Ar} \\ \searrow \text{R}_1 \end{array} \end{array} $			Analgesic Activity in Rats		
			$x = 2$	$x = 2$	$x = 3$
<u>R</u>	<u>R₁</u>	<u>Ar</u>	<u>y = 1</u>	<u>y = 2</u>	<u>y = 2</u>
Me	CO ₂ Et	Ph	inactive	1	0.3
Me	COEt	<u>m</u> -HO-Ph	-	10	0.7
Me	SO ₂ Et	Ph	-	(in mice)	0.3

STEREOCHEMISTRY OF PETHIDINE AND RELATED COMPOUNDS

Pethidine, itself is a symmetrical molecule. The only compound in this series in which enantiomers have been studied is phenoperidine (6), in which the asymmetric centre is located in the N-substituent (Mazur 1961).



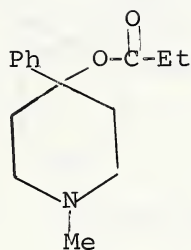
The (-) enantiomer is twice as active as the racemate in mice and about four times as active as the (+) isomer.

The seven-membered ring analogue of pethidine has been resolved and preliminary results indicate that most of the analgesic activity resides in one of the isomers (Diamond 1957).

Patent literature (Janssen 1961) contains a reference to synthesis of 3-methyl analogues of pethidine. These are discussed later in detail.

REVERSED ESTERS OF PETHIDINE AND RELATED COMPOUNDS:

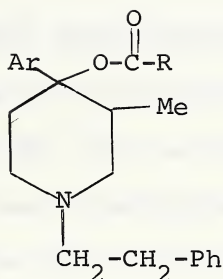
When a 4-carbalkoxy group in the pethidine type of compound is replaced by a 4-acyloxy group, the new compounds so obtained are referred to as reversed esters of pethidine. Lee (1951) first reported the synthesis



of the reversed ester of pethidine (7) and found it to be approximately 30 times more potent than pethidine (Jensen et. al. 1943; Foster and Carman 1947).

Maintaining the optimal substitution of the propionoxy residue in 4-phenyl-4-propionoxy-N-methylpiperidine (lower and higher acyloxy derivatives are less active), Ziering et. al. (1947) introduced a methyl group in the 3-position of the piperidine ring yielding two diastereoisomers, designated α - and β -prodine (α -generally denotes the more abundant isomer and has no stereochemical connotation unlike steroid α/β nomenclature). The β -isomer was approximately 7 to 8 times more potent than the corresponding α -isomer in rats (Randall and Lehmann 1948).

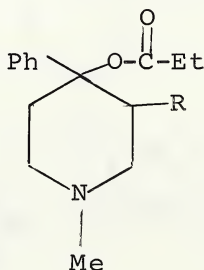
Beckett and coworkers (1959) have reported the synthesis of N-2-phenethyl-4-aryl-4-acyloxy-3-methylpiperidine (8) compounds.



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Pharmacological results indicate that the N-2-phenethyl compounds are more potent analgesics than the corresponding N-methyl compounds. It is interesting to note, that in N-2-phenethyl-4-phenyl-4-acyloxy-3-methylpiperidine compounds, the acetoxy esters are more potent than the corresponding propionoxy esters whereas the reverse is invariably true in unsubstituted reversed esters of pethidine and in esters prepared from 4-aryl analogues of the prodine alcohols (Beckett and coworkers 1957).

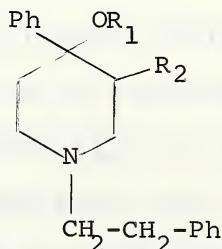
Randall and Lehmann (1948) reported that the activity of 3-ethyl-1-methyl-4-phenyl-4-propionoxypiperidine (no information concerning isomers is given) was 6.4 times that of morphine. Thus in analgesics of formula (9), activity increases with the increasing size of the 3-substituents (H to Et).



9

McElvain and Barnett (1956) have synthesized and tested the next higher homologue ($R=n\text{-Pr}$) which has activity in rats at doses of 8 mg./Kg. but no direct comparison has been made with the lower homologues and it is therefore, not possible to draw any conclusions with regard to the optimal size of the 3-substituent from this evidence. Large groups in the 3-position such as benzyl completely abolish activity. (McElvain and Barnett 1956). Benson et. al. (1957) have observed that the 3-allyl analogue of prodine is approximately 10 times as active as α -prodine with no corresponding increase in its toxicity.

Beckett and coworkers (1959), however, conclude from their studies on N-phenethyl-3-alkyl-4-phenyl-4-acyloxypiperidine compounds (10), that with few exceptions, optimum activity in respect to 3-alkyl substitution is afforded by a methyl group.



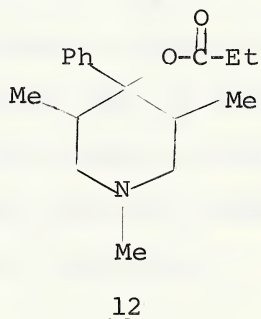
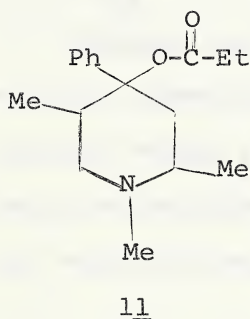
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where $\text{Ph}=\text{C}_6\text{H}_5$, $\text{o-Me-C}_6\text{H}_4$, or $\text{m-Me-C}_6\text{H}_4$ -

$R_1 = \text{H}$, $-\text{COMe}$, or $-\text{COEt}$

$R_2 = \text{H}$, Me , Et , or $n\text{-Pr}$

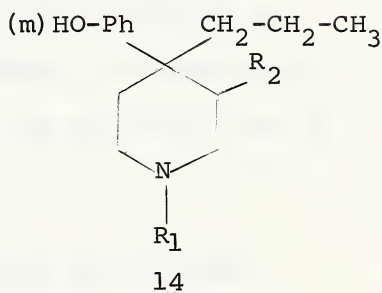
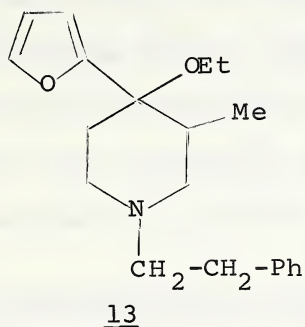
Nazarov and coworkers (1956) have prepared three of the four possible racemates of 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine (11). Promedol, which is one of the isomers (γ), has been reported to be several times more potent than pethidine. Another stereoisomer known as isopromedol (α -isomer) is 2 to 3 times more potent than promedol and has been approved for clinical use in U.S.S.R.



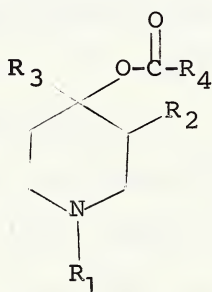
The three theoretically possible diastereoisomers of 1,3,5-trimethyl-4-propionoxy-4-phenylpiperidine (12) have been synthesized by Sorokin (1961). The most potent (γ) isomer is comparable to promedol in activity whereas α - and β -racemates are inactive.

The pharmacological results indicate that substitution of 4-alkoxy group as in 4-ethoxy-4-(2-furyl)-3-methyl-1-phenethylpiperidine (13) or a non-polar hydrocarbon residue of the appropriate size as in 4-m-hydroxyphenyl-4-propylpiperidine compound (14) for the polar oxygenated function usually found in the 4-position still

maintains good morphine-like activity (Casy 1961; McElvain and Clemens 1958).



Harper and Fullerton (1961) studied a series of ethynyl, phenethynyl and styryl compounds (15) of the prodine series to determine whether the aromatic ring could be replaced by other groups which were not aromatic but which possessed a π cloud of electrons.



where $R_1 = \text{Me}$, or $\text{CH}_2\text{-CH}_2\text{-Ph}$

$R_2 = \text{Me}$ or H

$R_3 = \text{CH}\equiv\text{C-}$, $\text{Ph-C}\equiv\text{C-}$ or Ph-CH=CH-

and $R_4 = \text{Me}$ or Et .

Only the 4-phenethynyl derivative showed pronounced pharmacological activity which has been judged to possess general central nervous depressant properties rather than

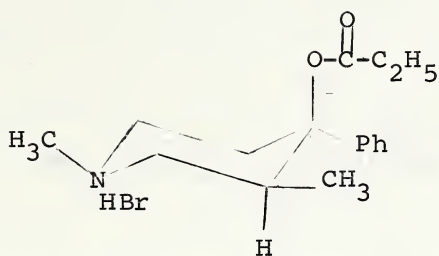
morphine-like activity. This survey includes several examples of diastereoisomers where analgesic properties vary amongst various isomers. Hence, stereochemical features have an important influence upon activity in 4-phenylpiperidines and it is therefore, of importance to have knowledge of configurations and conformations of asymmetric examples.

CONFIGURATIONAL ASSIGNMENTS OF PRODINES AND RELATED COMPOUNDS:

The 3-alkyl-4-phenyl-4-hydroxypiperidines possess two asymmetric centres and thus two diastereomeric racemates are possible. The stereochemistry of these isomers has been studied extensively for α - and β -prodine. Conflicting views existed before 1959, regarding configurational assignments to α - and β -1,3-dimethyl-4-phenyl-4-propionoxypiperidine.

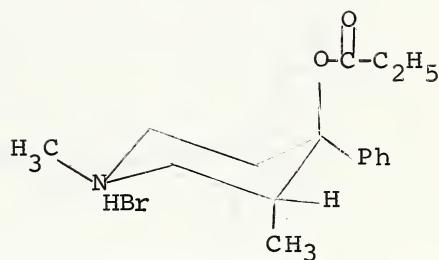
With the object of resolving this configurational problem, Ahmed et. al. (1959) undertook an X-ray crystallographic study of dl- α -prodine and dl- β -prodine salts. X-ray studies establish that in dl- α -prodine hydrobromide (16) the piperidine ring exists in the chair form with the 4-phenyl and 3-methyl groups in equatorial and the propionoxy chain in axial positions; therefore 3-Me is trans to the 4-Ph group.

Ahmed et. al. (1962) also studied the X-ray crystal



dl - α - Prodine HBr

16

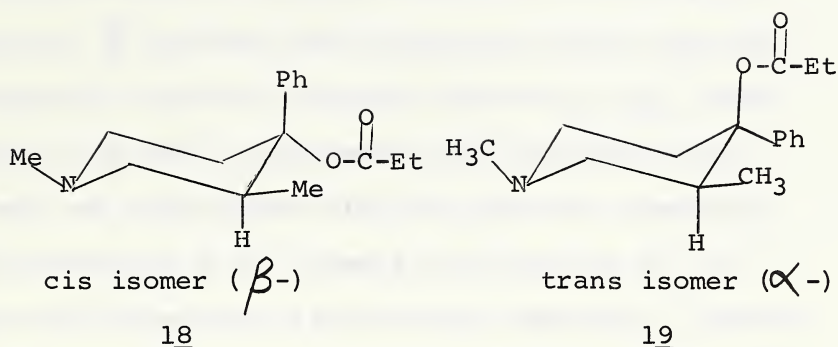


dl - β - Prodine HBr

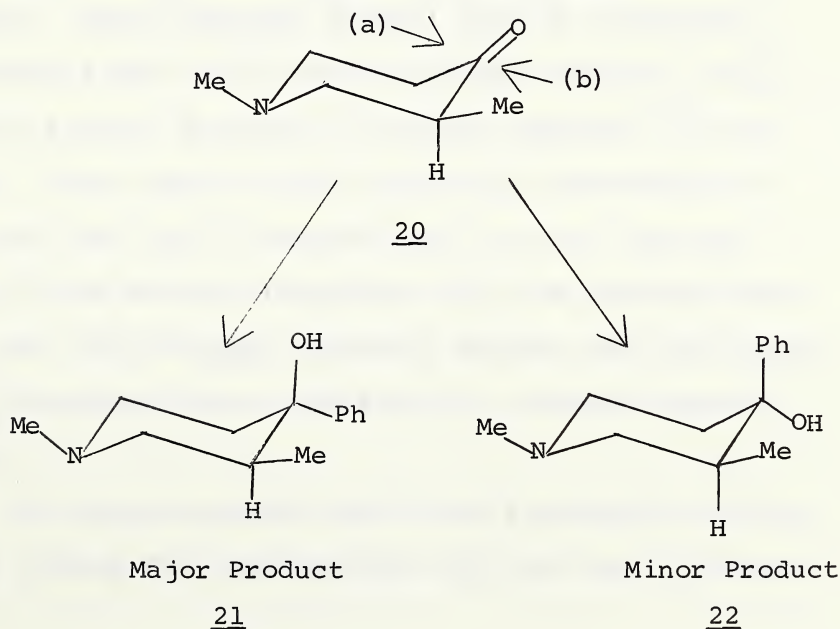
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structure of dl- β -prodine hydrobromide (17). The X-ray data indicate that here the piperidine ring has the chair form with the 4-phenyl group still in an equatorial, and the 4-propionoxy chain in an axial position but the 3-Me group is axial and thus bears a cis arrangement to the 4-Ph group. In summary, α -prodine is the trans (3-Me/4-Ph) and β -prodine the cis (3-Me/4-Ph) isomer.

The chemical data is in general agreement with the configurations determined by the X-ray studies. Beckett and coworkers (1955) measured the hydrolysis rates of α - and β -prodine and found the β -ester to be hydrolysed the faster (the rates of the α - and β -N-phenethyl analogues differed in the same way). These workers interpreted their results in terms of the α -ester having an axial (less accessible) and the β -ester an equatorial propionoxy function as (18) and (19). If 3-Me is taken to be equatorial in both isomers, cis and trans 3-Me/4-Ph configurations follow.



Beckett et. al. (1957) also analyzed the stereochemistry of ArLi additions to 3-(e)Me-4-piperidone and concluded that the trans (3-Me/4-Ph) isomer should be formed in larger amounts since attack from the least hindered side (b) would be favoured.



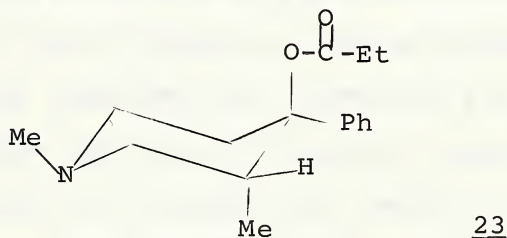
The reaction product yielded the ratio of 3:1 of α -prodine to β -prodine thus supporting their previous assignments. Further evidence (Beckett et. al. 1959) in support of their assignments was provided by the treatment of piperidones with various ArLi compounds. The predominance of α -isomers was expected to increase with increasing size of aryl addendum. Isomeric ratios obtained experimentally were in accord with these postulations. The addition of lithium phenyl, m- and p-tolyl compounds to piperidones gives isomeric mixtures in which one isomer predominates whereas the addition of lithium o-tolyl, o-methoxyphenyl and 2,6-dimethylphenyl results in virtually one pure isomer.

Casy (1961) studied the products obtained by the reaction of thionyl chloride with α - and β -prodine alcohol. The α -prodine alcohol gave an eliminated compound as the chief reaction product whereas the β -prodine alcohol produced a 4-chloro compound in high yield. These results were originally interpreted to indicate that the α -compound has an axial hydroxyl group (since facile elimination is to be expected when 4-OH and 3-H are trans oriented) whereas the corresponding β -compound has an equatorially oriented hydroxyl group.

The above evidence led to the formulation of the trans (3-Me/4-Ph) configuration (19) for the α -isomer.

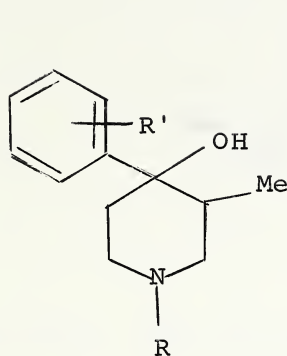
The configuration assigned to the α -isomer (19) and the equatorial and axial dispositions of all the substituents are in complete agreement with the X-ray studies. However, in the corresponding β -isomer, although the configuration (18) assigned by Beckett and his associates is identical with the X-ray conclusions, the axial and equatorial dispositions of the 3- and 4- substituents are the reverse of those found for the crystalline salt.

It is interesting to note that Archer (1958) after reviewing the chemical evidence proposed structures (19) and (23) for α - and β -prodine respectively.

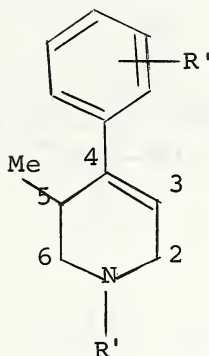


PMR investigations (Casy 1966) have now shown that the conformations (19) and (23) are preferred for α - and β -prodine, respectively, as solutes in CCl_4 and CDCl_3 (see later).

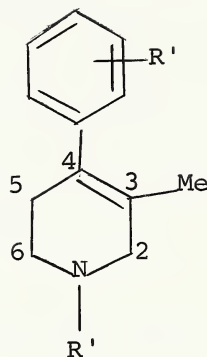
Casy et. al. (1965) studied the elimination of water from α -4-aryl-3-methyl-4-piperidinols (24). These alcohols were dehydrated by treatment with a mix-



24

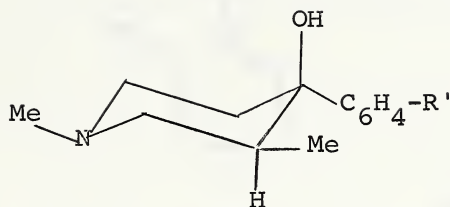


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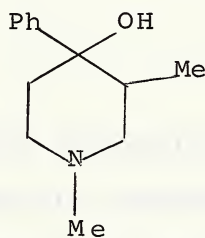
ture of acetic acid and hydrochloric acids at the reflux temperature. The binary mixtures of alkenes which resulted were analyzed by PMR spectroscopy. In mixtures derived from 4-phenyl, o- and m-tolylpiperidinols, the major component was a 5-methyl-1,2,5,6-tetrahydropyridine (25) characterized by signals due to vinylic hydrogen (a triplet) and 5-methyl (a doublet) in the PMR spectra and the minor component by a 3-methyl-signal (a singlet) and by the absence of a vinylic hydrogen signal. As the elimination probably follows a trans diaxial stereochemical course, the 3- and 5-methyl isomers formed from the α -isomer suggest axial hydrogen atoms are available at both the 3- and 5-positions in this isomer. The above evidence would suggest structure (27) for the α -4-aryl-3-methyl-4-piperidinols which completely supports the X-ray conclusions



27

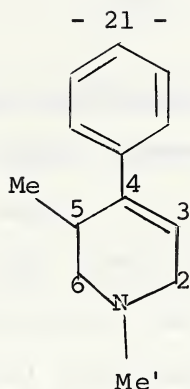
for the α -isomer.

Casy and coworkers (1967) also studied the elimination of β -1,3-dimethyl-4-phenyl-4-piperidinol (28). When this compound was heated at 50-52° with



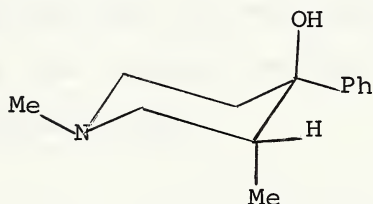
28

16-17% aqueous hydrochloric acid for 24 hours, the 5-methyltetrahydropyridine (29) was obtained in 80% yield. If a trans diaxial orientation of the substituents is assumed to be the stereochemical requirement for elimination, the exclusive formation of the 5-methyl isomer suggests the presence of an axial H-atom only at 3-



29

position. This evidence would suggest structure (30)



30

for the β -1,3-dimethyl-4-phenylpiperidinol. This conclusion is also in complete agreement with the X-ray studies. It may be noted here that under the described mild dehydration conditions α -prodine failed to eliminate water.

In an attempt to find a more convenient physical method than that of X-ray crystallography to assign correct configurations to diastereoisomeric pairs, Casy (1966) studied the PMR spectra of the alcohols derived from α - and β -prodine and showed that differences in

the spectra allowed configurational and conformational assignments to be made. These findings will be discussed in detail later.

Ziering et. al. (1947; 1957) earlier suggested the reverse configurations for α - and β -proline on the basis of spatial relationship of dihydrodeoxymorphine-D to one of the more potent isomers and the interpretation of the infrared spectra of the two isomers. Their conclusions are not supported by other physical methods such as X-ray crystallography, and PMR spectroscopy, the chemical evidence and/or the stereochemical considerations.

THE INFLUENCE OF CONFIGURATION UPON ANALGESIC
ACTIVITY IN 4-PHENYLPYPERIDINES

The stress laid on the stereospecificity of drug action in terms of drug-receptor interaction assumes significance only if the more active isomers of stereoisomeric pairs are shown to possess common configurational features. Several such studies relating the more active isomers of enantiomorphous pairs to a common configuration have already been reported (Beckett and Casy 1955; 1957; Beckett and Anderson 1960; Beckett et. al. 1962; Pohland et. al. 1963; Casy and Myers 1964; and Portoghesi 1964).

Ziering and coworkers (1957) during their studies on 1,3-dialkyl-4-phenyl-4-propionoxypiperidine compounds have stated that there seems to be little relationship between stereochemistry and analgesic activity. This opinion appears to be naively conceived in view of the marked stereochemical selectivity shown by the diastereoisomers in the 3-methyl, 3-ethyl, 2,5-dimethyl, and 3,5-dimethyl reversed esters of pethidine, as already outlined. Some further data are shown in Table IV, examination of which shows that all the more potent members of the diastereoisomeric pairs have the β - (cis 3-Me/4-Ph) configuration.

Beckett et. al. (1959) reported the corresponding diastereoisomeric N-2-phenethyl pair of analogues and

showed that these compounds differ in activity in the same sense. Thus, cis N-2-phenethyl-3-methyl-4-phenyl-4-propionoxypiperidine (31) is approximately 5 times as active as the trans isomer (32).

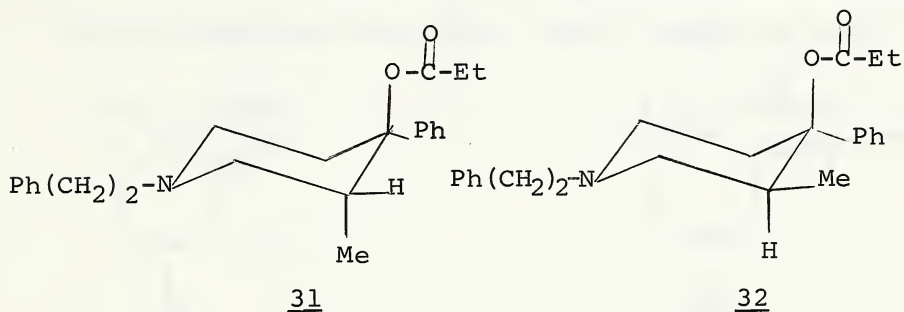
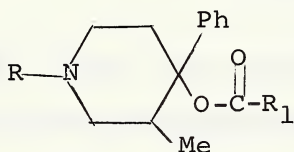
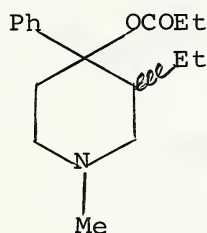


TABLE IV. ANALGESIC ACTIVITIES IN MICE OF SOME DIAS-TEREOMERIC ESTERS OF 3-ALKYL-4-PHENYLPYPERIDINOLS:
(HOT PLATE TEST) (Casy 1968)

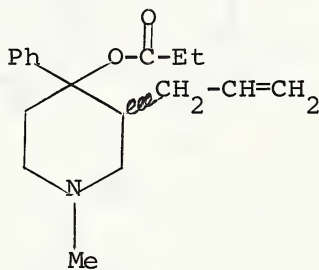


<u>No</u>	<u>R</u>	<u>R₁</u>	<u>Isomer</u>	<u>Potency Ratio</u> <u>Morphine 1</u>
1.	Me	Me	α	0.4
	Me	Me	β	2.2
2.	Me	Et	α	2.0
	Me	Et	β	8.7
3.	Me	n-Pr	α	1.3
	Me	n-Pr	β	2.9

Ziering et. al. (1957) reported the synthesis of N-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine diastereoisomers. Here also the β -(configuration not established) isomer (33) is (1.2 times) more active than the corresponding α -isomer. In N-methyl-3-allyl-4-phenyl-4-propionoxypiperidine (34), the α -isomer is more



33



34

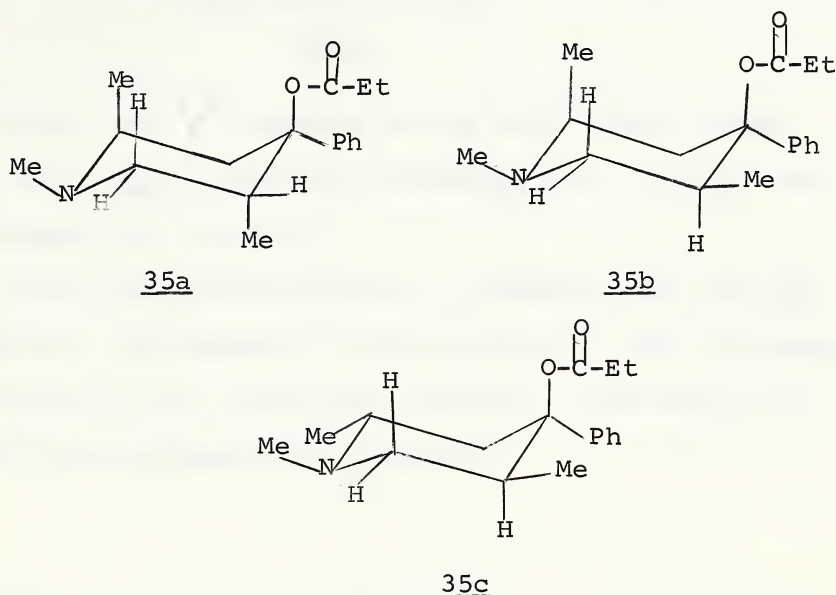
active than the corresponding β -isomer. It must be noted here that the stereochemistry of the α/β 3-Et and 3-Allyl isomers has not been unequivocally established.

Casy et. al. (1961) have synthesized N-2-phenethyl-4-ethoxy-4-(2-furyl)-piperidine (13). It is noteworthy that this compound, a potent analgesic, has the cis configuration. The trans isomer is not available for comparison in this case.

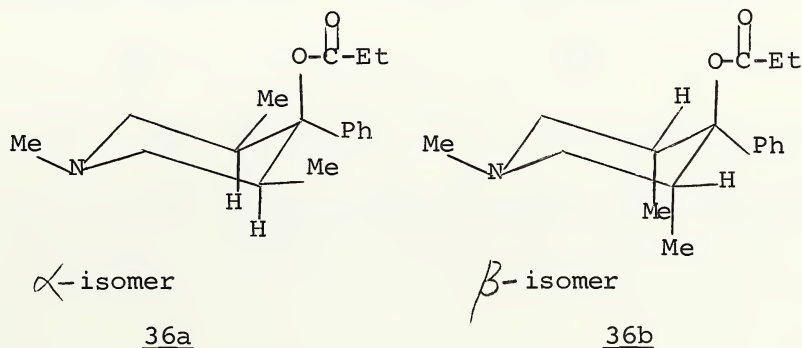
Nazarov and coworkers (1956) prepared three of the four possible racemates of 1,2,5-trimethyl-4-phenyl-4-propionoxypiperidine (11).

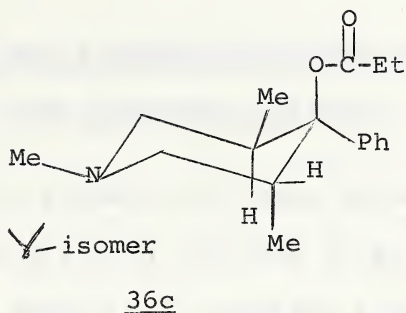
The complete stereochemical assignment of these diastereoisomeric racemates has been reported (Prostakov

1964) and their configurations are depicted in the e-Ph conformations 35a, 35b and 35c. It is interesting to note that the most active compound is the α -isomer which has a cis (3-Me/4-Ph) configuration.



The three possible diastereoisomers of 1,3,5-trimethyl-4-propionyloxy-4-phenylpiperidine (12) have been prepared by Sorokin (1961). The stereochemical assignments of the three racemates are as given below:



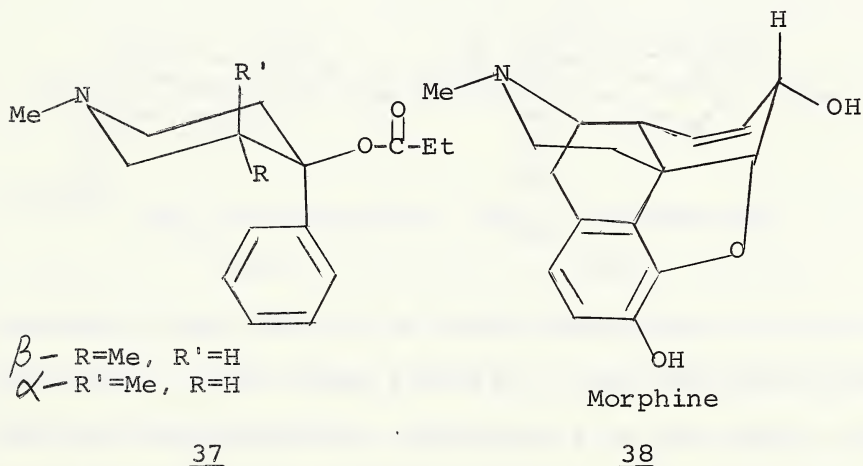


Here again, the γ -racemate is the most active isomer which has a cis (3-Me/4-Ph) configuration. The α - and β -isomers are inactive.

From the above evidence, it appears that the cis (3-Me/4-Ph) arrangement is more effective than the trans configuration as a structural feature in analgesically active 4-phenylpiperidine molecules.

INFLUENCE OF THE 4-PHENYLPYPERIDINE CONFORMATION
UPON ANALGESIC ACTIVITY

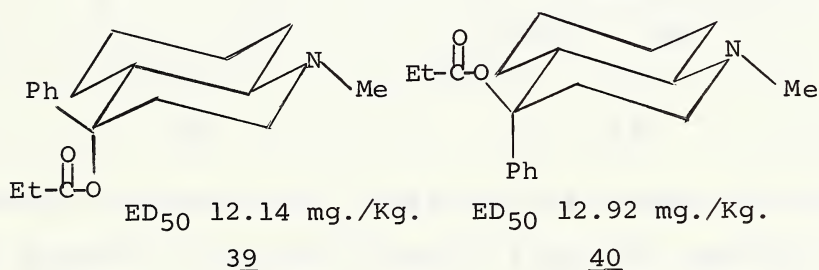
Substantial evidence has been presented which supports the superiority in activity of cis 3-Me/4-Ph over trans 3-Me/4-Ph geometry in reversed esters of pethidine. The next point to be considered is whether activity variations between diastereoisomers of this class may be attributed to conformational differences. The original proposals regarding structural features of the analgesic receptor (Beckett and Casy 1954) imply that β -prodine is more active than the α -form because the population of the axial phenyl conformer is likely to



be greater in the β -isomer (α -37 is destabilized by an axial 3-Me group); conformational resemblance to the rigid model, morphine (in which the molecule is

constrained to an axial phenyl chair conformation) will then be greatest in β -proline.

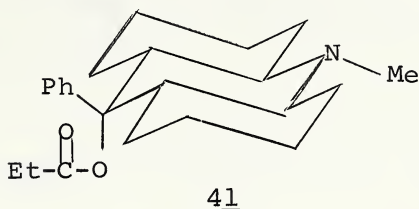
The necessity of an axial aromatic function as a requirement for analgesic action is, however, highly controversial. In an attempt to resolve this controversy, Smissman and Steinman (1966) designed a rigid system in which the only variable (in their view) was the conformation of the aromatic group. These workers selected 1-methyl-4-phenyl-4-propionoxydecahydroquinoline isomers (39) and (40) for reasons of close comparison to the work of Beckett and Casy (1954). These



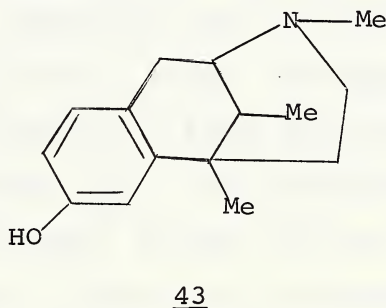
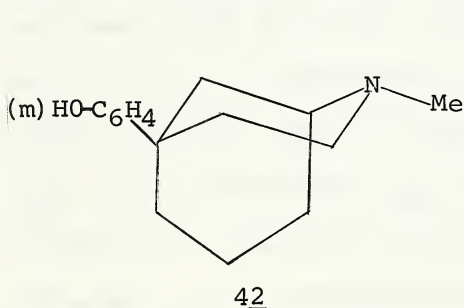
compounds were found to be almost equipotent in mice as analgesics. From these results, it was concluded that no definite conformational requirements of the phenyl group were essential for analgesic action.

In order to further substantiate their view-point, the same authors (Smissman and Steinman 1967) attempted to prepare two perhydroacridine analogues. Only one

isomer (41) was obtained and this proved to be inactive.

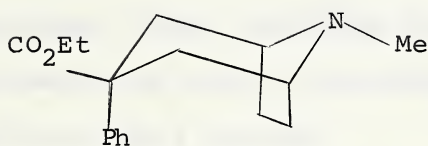


Portoghese (1966) has also advanced views upon conformational influences in 4-phenylpiperidine analgesics and cites the example of the azabicyclononane derivative (42). In this compound, although the trimethylene bridge

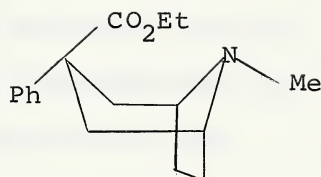


prevents conformational inversion, and thereby precludes the presence of an axial aromatic ring, the compound has potency comparable to the phenolic benzomorphan structure (43) in which the phenyl group is axial with respect to the piperidine ring.

Bell and Archer (1960) synthesized the tropane analogue of pethidine (44a) and found it to be slightly more active than pethidine. The same authors have shown by spectral evidence that there is a substantial amount of boat conformation (44e) present. Portoghese and his as-

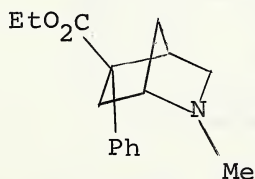


44a

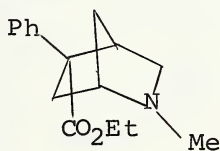


44e

sociates (1966) have provided evidence demonstrating that a boat conformation may be the active form for the bicycloheptane analogues of pethidine. In these diastereoisomers (45) and (46), the piperidine ring is rigidly held in a boat conformation by the C₇ group. The endo phenyl compound (45) is approximately 6 times more potent than the corresponding exo isomer (46). The difference in activity, however, is attributed, in part, to the differences in the concentrations in which the two isomers



45



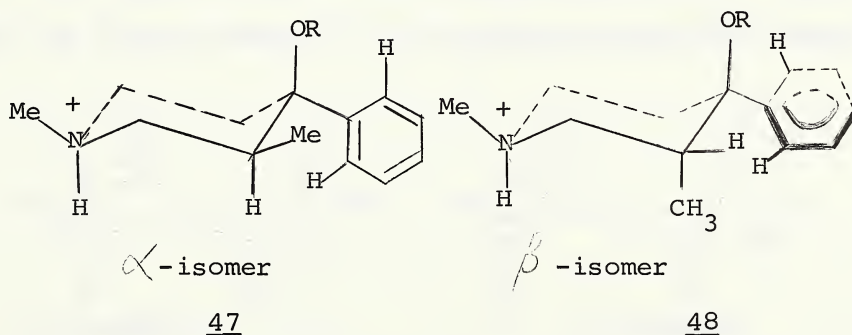
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reach the site of action.

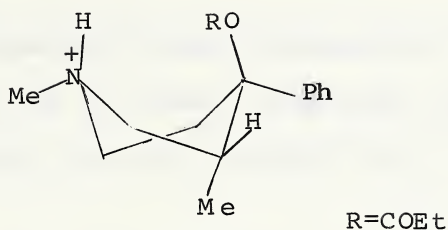
On the basis of this evidence, and the opinion of Ziering and coworkers (1957) that there was little rela-

tionship between stereochemistry and analgesic activity, Portoghesi (1966) concluded that the conformational requirements for most of the 4-phenylpiperidine type analgesics were minimal.

In order to obtain more evidence upon the significance or otherwise of conformational requirements in 4-phenylpiperidine analgesics, Casy (1968) studied the probable conformations of some reversed esters of pethidine as solutes in D_2O (data of relevance also to water, the medium of greatest biological importance). On the basis of PMR data of acetate, propionate, and *n*-butyrate esters of α - and β -1,3-dimethyl-4-phenyl-4-hydroxypiperidine hydrochlorides, the most probable conformations of the α - and β -isomeric ester hydrochlorides in $CDCl_3$ were shown to be (47) and (48) respectively.



However, while α -esters have similar conformations in both $CDCl_3$ and D_2O ; the β -esters in D_2O are considered to adopt preferred skew-boat conformations (49) (details later).

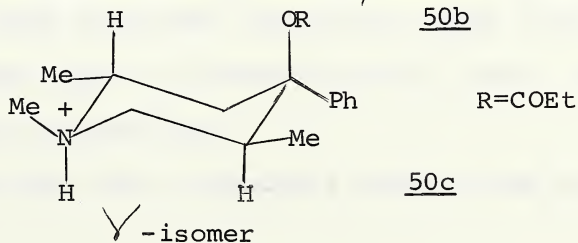
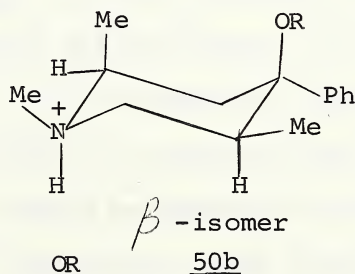
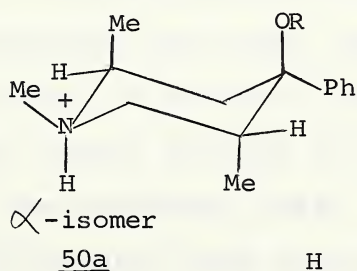


β -isomer

49

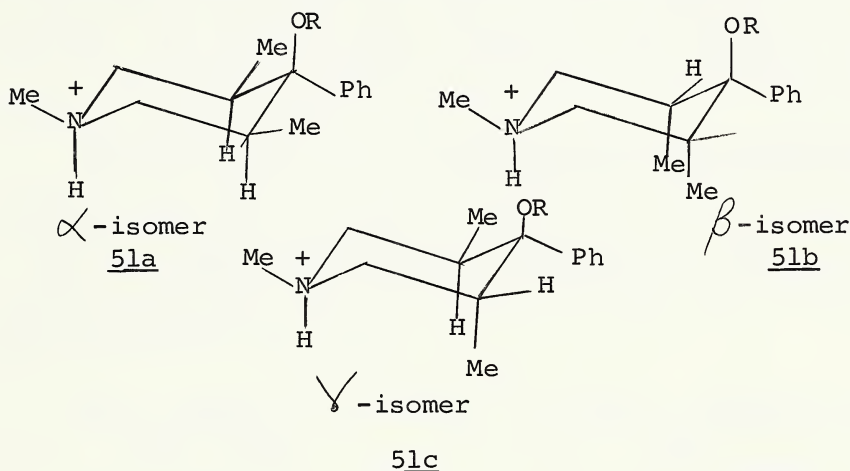
In the light of these observations and the fact that the α -isomers (in which a non-chair conformation is improbable), are less potent than β -forms, Casy (1968) postulated that the skew-boat conformation represents an optimum arrangement of structural features in 4-phenylpiperidine analgesics and that the derivatives which might be expected to have high skew-boat populations may well be potent compounds. This postulate is supported by the following examples:

1. Of the three isomeric 1,2,5-trimethylpiperidine esters,



the skew-boat conformation is most favoured in the α -isomer and least in the γ -isomer, compounds with the highest and the lowest activity, respectively, among the trio.

2. In the 1,3,5-trimethyl derivatives, factors unfavourable toward a skew-boat conformer obtain in all the iso-



mers (non-bonded interactions of \underline{e} -Me groups in α - and γ - are raised in boat forms and models show that the cis 1,3-diaxial interaction of β - is not relieved in the corresponding boat form), the sole active member (γ -) being about as active as the γ -1,2,5-trimethyl isomer.

3. The tropane analogue of pethidine is somewhat more potent than pethidine itself. It would be expected to have a significantly large skew-boat population (44e) since the chair conformer (44a) is destabilized by axial - Ph bimethylene bridge interactions.

It was concluded that although a fairly wide range of

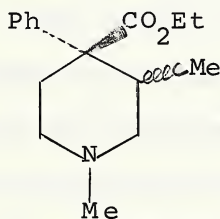
4-phenylpiperidine conformations were compatible with activity, those in which the aromatic and piperidine rings approach coplanarity (as in the skew-boat with phenyl in the bow-sprit position) may be most effective in evoking a response.

AIMS AND OBJECTS OF THE PRESENT WORK

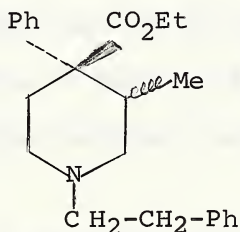
It is evident from the preceding literature survey that whereas the effect of substituents in the 3-position in reversed esters of pethidine has been studied in detail, the influence of substitution in the 3-position of pethidine itself has not been systematically investigated. In view of this, a study of the 3-methyl analogues of pethidine was planned.

Specific pairs of diastereoisomers considered for synthesis and pharmacological evaluation were as follows:

1. Cis and trans (3-Me/4-Ph)-1,3-dimethyl-4-phenyl-4-carbethoxypiperidine (52)



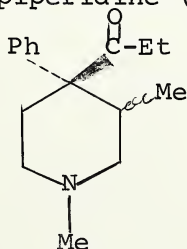
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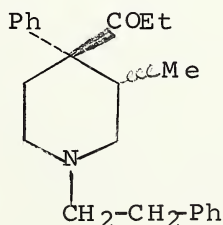
53

2. Cis and trans (3-Me/4-Ph)-N-2-phenethyl-3-methyl-4-phenyl-4-carbethoxypiperidine (53).

3. Cis and trans (3-Me/4-Ph)-1,3-dimethyl-4-phenyl-4-propionypiperidine (54).



54



55

4. Cis and trans (3-Me/4-Ph) -N-2-phenethyl-3-methyl-4-phenyl-4-propionylpiperidine (55).

The N-phenethyl derivatives (53) and (55) were included because it has been shown that in general these are more active than the corresponding N-methyl compounds. Hence activity differences between α / β pairs should be more pronounced in the N-phenethyl congeners.

The esters would be synthesized from the 4-cyano intermediates. This function may readily be converted to 4-propionyl and hence such derivatives have been included because of their synthetic availability and also because active compounds containing this function are known (e.g. Ketobemidone).

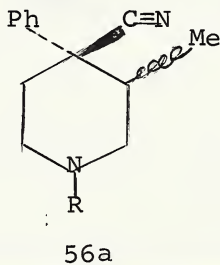
The object of the above programme was to provide further data relating to the influence of both configurational and conformational factors upon analgesic activity in 4-phenylpiperidine derivatives.

Certain minor objectives, which developed during the course of the experimental work relating to the main series, are described at appropriate sections of the thesis.

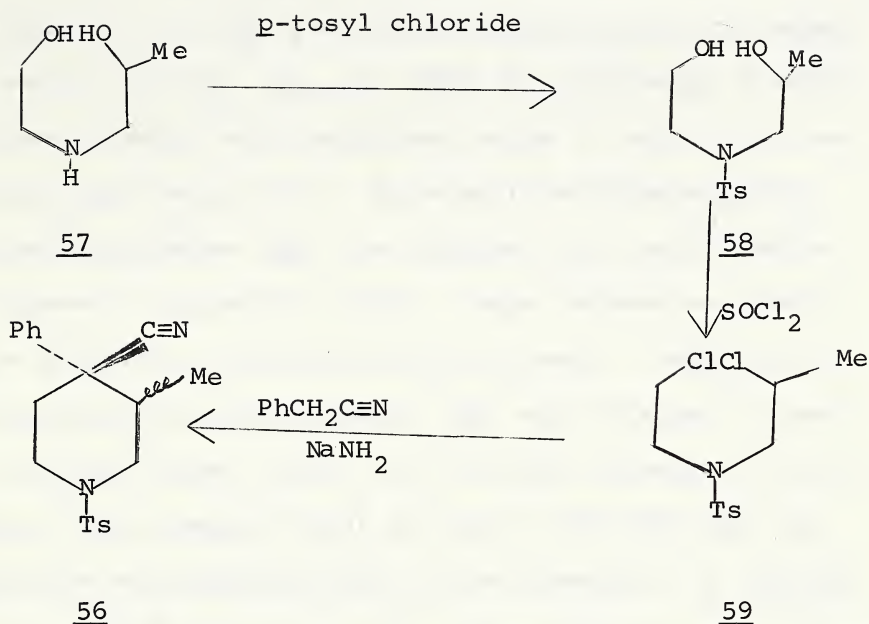
DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

At the outset of the present work, it was clear, from knowledge of the synthesis of pethidine itself, that the key step in the route, leading to the synthesis of desired compounds (mentioned in the last section) was the successful synthesis and separation of cis and trans N-substituted-3-methyl-4-phenyl-4-piperidinonitrile (56a) where R may be a group which could be easily replaced by



a biologically useful alkyl group(s). In the conception of the synthetic approach, it was desirable that the basic nitrogen centre be blocked with a protective group which would withstand the rigors of reactions employed in the synthetic sequence and be capable of being removed without affecting other substituents in the molecule. The tosyl and benzyl groups fulfilled these requirements. A literature search revealed that compounds of this nature have been reported in the patent literature by Janssen in 1963, the N-substituent being the *p*-toluene sulphonyl (tosyl) group; the route to these derivatives, starting from N- β -hydroxyethyl-N- β -hydroxypropylamine (57) is shown on the next page:-

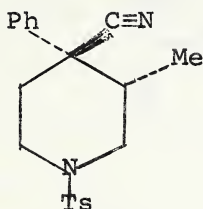


The N-tosyl nitrile (56) was obtained in isomeric forms, one insoluble in methanol (designated β -) and the other soluble in the same solvent (designated α -). Janssen (1963) assumed the α -isomer to have the trans (4-Ph/3-Me) configuration on the basis of an empirical solubility rule. Much of the earlier work on which this rule is based suffered from both inadequate product analysis and isomerization of initially formed products. As a result it is unwise to consider this rule a reliable criterion for stereochemical assignments (Wicker 1956).

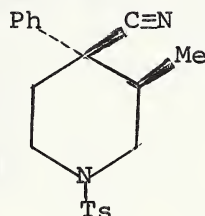
The starting material, N- β -hydroxyethyl-N- β -hydroxypropylamine (57) was commercially available and was used as such without further purification. At a later stage,

when the company failed to supply the pure material, it was prepared in high yield by a modification of a reported method (Cottle, et. al. 1946) by condensing 2-aminoethanol (4 mole) with propylene oxide (1 mole) (the reported ratio being 9:1). N-p-tosyl-2-hydroxyethyl-2-hydroxypropylamine (58) was prepared by a modification of Janssen's procedure (1963). Here benzene was found to be a superior recrystallizing solvent. N-p-Tosyl-2-chloroethyl-2-chloropropylamine (59) was obtained by heating the diol under reflux with thionyl chloride in chloroform. This compound (59) melted at 118-120° and its structure was substantiated by the absence of a hydroxy peak in its IR spectrum and by elemental analyses. Janssen (1963) did not report the melting point of this compound (59) which is very difficult to crystallize; in subsequent reactions the crude material was used. Various attempts were made to cyclize N-p-tosyl-2-chloroethyl-2-chloropropylamine with phenylacetonitrile using sodium hydride or sodamide as condensing agents but all attempts to obtain the pure isomers either by preferential solubility in methanol (as in Janssen's patent) or column chromatography were unrewarding. However, later attempts (carried out after β -N-tosyl-3-methyl-4-phenyl-4-piperidinonitrile had been synthesized by an independent route) (see later) to cyclize the N-tosyl dichloro compound (59) with the phenylacetonitrile anion using sodamide as a condensing agent and toluene as a solvent were

successful. The reaction product in boiling methanol deposited a solid, m.p. 217-218° which corresponded with the β -isomer (60) of the patent (Janssen 1963).



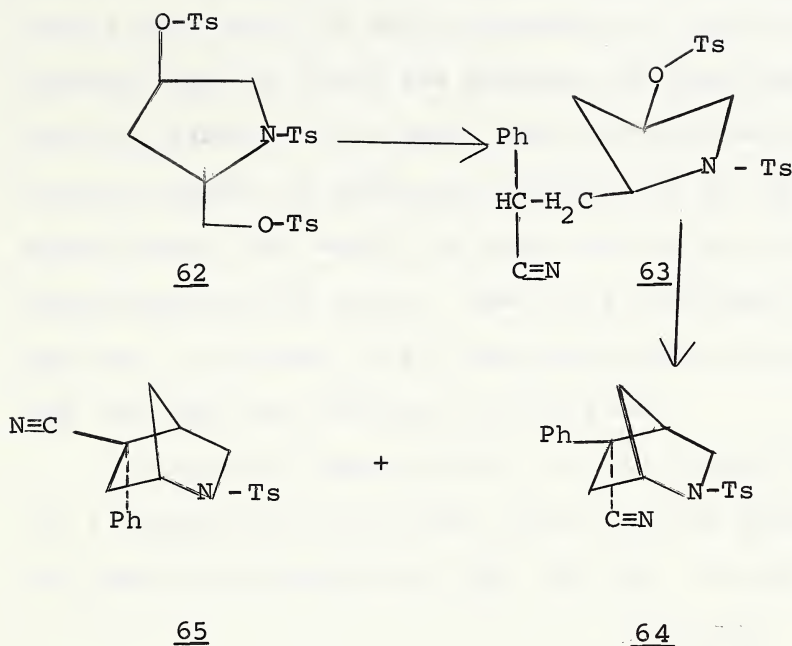
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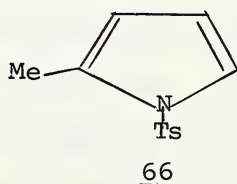
61

The methanol soluble isomer, which was obtained in pure form by column chromatography over alumina in a methylene chloride fraction and subsequent recrystallizations from methanol, melted at 149-149.5°. This isomer corresponded with the α -isomer (61) of the patent (Janssen 1963). The yields were generally low (especially those of the α -isomer) and reproducible results could not be obtained. Modifications of the patent procedure were, therefore, studied.

During the course of this work, Portoghesi and others (1968) reported the condensation of N,O,O-tritosylhydroxyprolinol with the phenyl acetonitrile anion. These workers envisaged that displacement of the primary tosyloxy group of (62) by phenylacetonitrile anion would afford an intermediate (63) which would subsequently undergo cyclization to (64) and (65) by internal SN_2 displacement of the secondary tosyloxy substituent. When

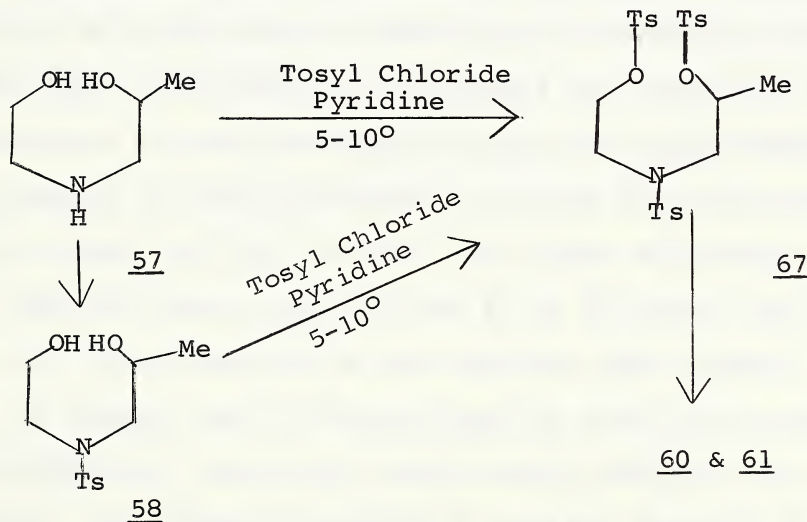


the cyclization reaction was carried out in the presence of two equivalents of sodamide and one equivalent of phenylacetonitrile in tetrahydrofuran, these workers were able to isolate one of the two possible isomeric products (64) in very low yield. A substantial quantity of another product was obtained which proved to be N-tosyl-2-methylpyrrole (66), probably formed by elimination of the tosyloxy substituents (by excess of sodamide) and subsequent isomerization. Consequently, four equiva-



lents of sodamide and five equivalents of phenylacetonitrile were used for each equivalent of N,O,O-tritosyl compound (62) to avoid the presence of free amide anion which by virtue of its small size and high basicity would be more capable of affecting elimination of the tosyloxy substituents than would the much bulkier and less basic phenylacetonitrile anion. When this modification was employed, a mixture of the desired epimeric products (64) and (65) was obtained in 75% yield.

In view of these results, it was decided to utilize a similar N,O,O-tritosyl route for the synthesis of the desired intermediates (60) and (61) as given below:

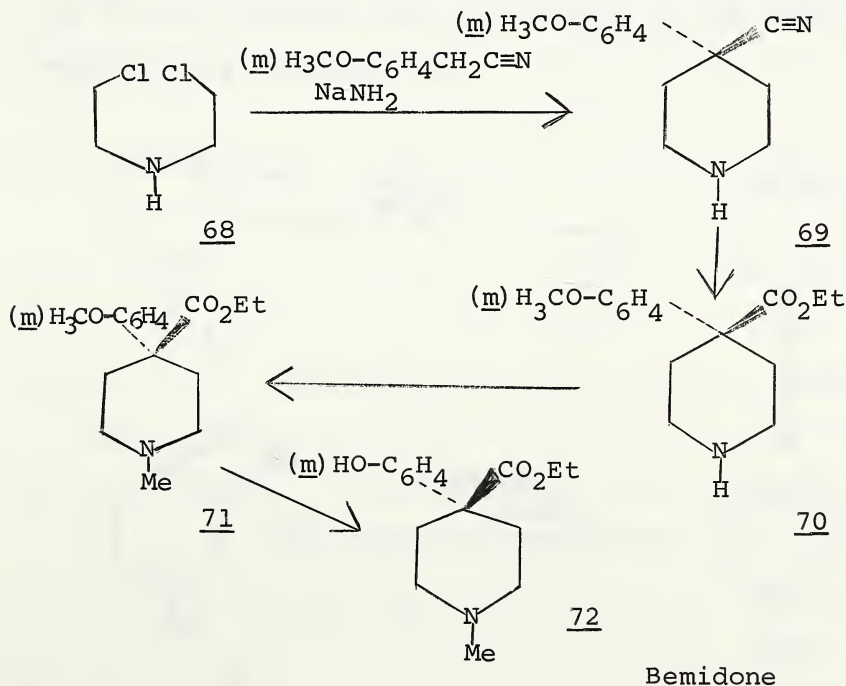


N,O,O-Tritosyl-2-hydroxyethyl-2-hydroxypropylamine (67) was synthesized by two routes. N-p-Tosyl-2-hydroxy-ethyl-2-hydroxypropylamine (58) was prepared as previously mentioned and O,O-ditosylated by reaction with p-tosyl chlor-

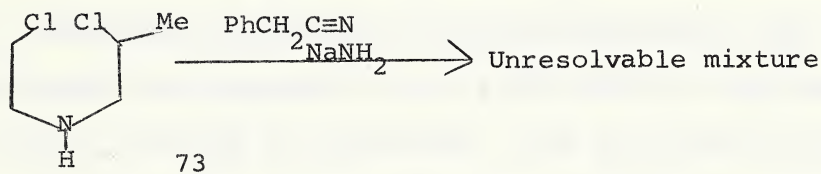
ide in pyridine (72 hr. at 5-10°) (this procedure was used by Portoghese et. al. (1966) for the synthesis of N, O,O-tritosyl-hydroxy- β -prolinol). The product obtained was a liquid and was purified by column chromatography over alumina. The structure of the product (obtained in a single fraction using benzene as an eluant) was established by its IR characteristics (i.e. absence of hydroxyl and N-H bands and the presence of 1350 and 1170 cm^{-1} bands attributed to asymmetric and symmetric stretching, respectively of SO_2) and elemental analyses. The same compound (67) was obtained in good yield by subjecting N- β -hydroxyethyl-N- β -hydroxypropylamine (57) directly to the pyridine-p-tosyl chloride procedure. The cyclization of N,O,O-tritosyl-2-hydroxyethyl-2-hydroxypropylamine (67) (1 equivalent) was carried out using five equivalents of phenylacetonitrile and four equivalents of sodamide in tetrahydrofuran following the conditions of Portoghese, et. al. (1968). An excess of sodamide in the reaction mixture was avoided so as to reduce the possibility of elimination of the tosyloxy substituents. The two isomers were isolated from the reaction mixture by preferential solubility method using methanol as a solvent. The isomer insoluble in boiling methanol on recrystallization from n-butanol melted at 217-218° and was identical with the β -isomer obtained previously as shown by IR spectral comparisons and the fact that no depression of melting point was observed on determining the mixed melting point. The other isomer soluble in boiling

methanol which was obtained by concentrating the methanol mother liquors was purified by recrystallization from methanol and melted at 148-149°. This compound was identical with the Δ -isomer (61) previously obtained by Janssen's procedure (1963). The isomers were obtained in about 55% yield (based on tritosyl compound), this yield being higher than that of the original method and reproducible. Henceforth, this sequence of reactions was employed as the method of choice for the synthesis of N-substituted 3-methyl-4-phenyl-4-piperidinonitrile diastereoisomers.

During the course of these investigations, a patent report (thr. Braenden et. al. 1954) was noticed which described the synthesis of bemidone (72) by the following sequence of reactions:

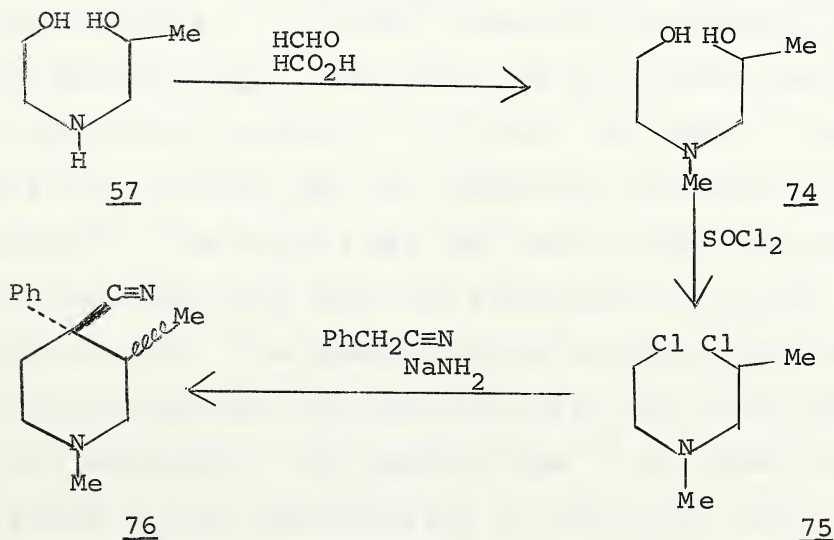


This route has the advantage of providing a secondary amine intermediate (70) directly. It could not be applied, however, in the present series since condensation between N- β -chloroethyl-N- β -chloropropylamine (73) and phenylacetoneitrile in the usual manner resulted in an unresolvable



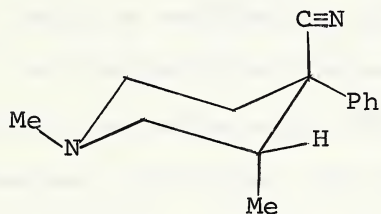
reaction product.

While difficulties were being experienced in obtaining pure diastereoisomers (56) from the N-tosyl route, the possibility of utilizing tertiary base analogues of the N-tosyl dichloro derivative (59) in the same reaction sequence was investigated.

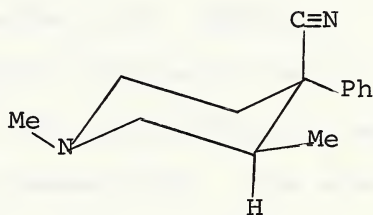


N-Methyl-2-hydroxyethyl-2-hydroxypropylamine (74) was prepared by $\text{HCHO-HCO}_2\text{H}$ reaction on N- β -hydroxyethyl-N β -hydroxypropylamine (57) according to Clark's general procedure (1933). This product (74) gave a picrate of melting point ($72-73^\circ$) close to that of the picrate of the same compound prepared in a different manner (Jones and Wilson 1949). N-Methyl-2-chloroethyl-2-chloropropylamine (75) hydrochloride was prepared in high yield (96%) by reaction with thionyl chloride in chloroform. The structure of the compound (75) hydrochloride was confirmed by IR data (OH band(s) absent; NH^+ band present) and elemental analyses. (Precaution should be taken while using this compound (75) It is very unpleasant and being a nitrogen mustard, has a strong lachrymatory effect). N-Methyl-2-chloroethyl-2-chloropropylamine (75) freshly liberated from its hydrochloride salt was treated with phenylacetonitrile in toluene using sodamide as a condensing agent. In this case, phenylacetonitrile, (0.50 mole) N-methyl-2-chloroethyl-2-chloropropylamine (75) (0.42 mole) and dry toluene were mixed together and sodamide (1.25 mole) was added in small portions with stirring when the temperature was maintained between $5-10^\circ$. The mixture was then heated under reflux, cooled, hydrolyzed with water and extracted with dilute hydrochloric acid. The aqueous portion was made basic with solid sodium hydroxide and extracted first with ether and then with chloroform. The residual base in the ether extract formed a solid hydrochloride in acetone-HCl which was

resolved by a preferential solubility method using acetone as a solvent. The acetone insoluble isomer on recrystallization melted at 275-276° and was assigned the β -(cis 3-Me/4-Ph) configuration (77). The acetone soluble isomer



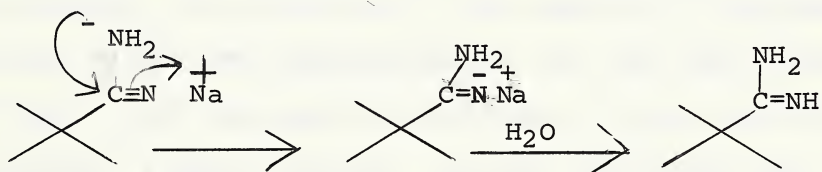
77



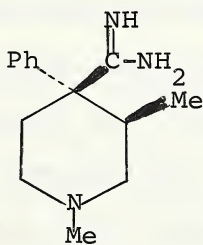
78

on recrystallization from ethyl acetate melted at 205-206° and was assigned the α -(trans 3-Me/4-Ph) configuration (78). The two isomers (separated and purified) were obtained in 88% yield (based on the N-methyl dichloro compound (75)), the yield of α -isomer (78) being considerably higher than the corresponding β -isomer (77). The stereochemical assignments were made on the basis of PMR data (see later). The residue obtained from the chloroform extract appeared to be a mixture of nitriles, amides and/or amidines, from the appearance of 2210, 1670, and 1630 cm^{-1} bands in the IR spectrum of the total product. Various attempts to resolve this mixture were unsuccessful. However, in one cyclization reaction, where excess of sodamide was used (same mode of addition) and the reaction allowed to proceed for a longer time, the major product isolated was a solid (m.p. 137-138°) which could be recrystal-

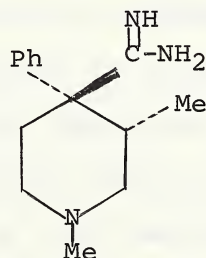
lized from benzene. This compound showed no $C\equiv N$ band, but bands in the $C=O$ and/or $C=N$ (1630 cm^{-1}) and OH/NH stretching frequency regions were present. The high nitrogen content of the compound excluded the possibility of its being an amide and, therefore, the likelihood of its being an amidine was given consideration. Amidines may be obtained from the corresponding nitrile by the attack of the amide anion (NH_2^-) upon the cyanide function and subsequent hydrolysis (Shriner and Newmann 1944). The ele-



mental analyses of the base itself corresponded with the amidine structure (79). This material formed a dihydrochloride as expected. On this basis, the band at 1630 cm^{-1}



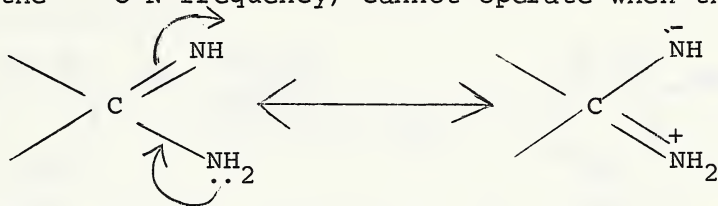
79



80

was assigned to $C=N$ of the amidine (Nakanishi 1962). This band shifted to a higher wave number (1670 cm^{-1}) when the amidine was protonated (35 cm^{-1} difference between the base and the hydrochloride both as nujol mulls), the dir-

ection of the shift showing the C=N bond to be less polar in the hydrochloride than in the free base. This may be explained by the fact that the resonance interaction of the free base (which effectively lengthens the C=N bond and lowers the C=N frequency) cannot operate when the amidine

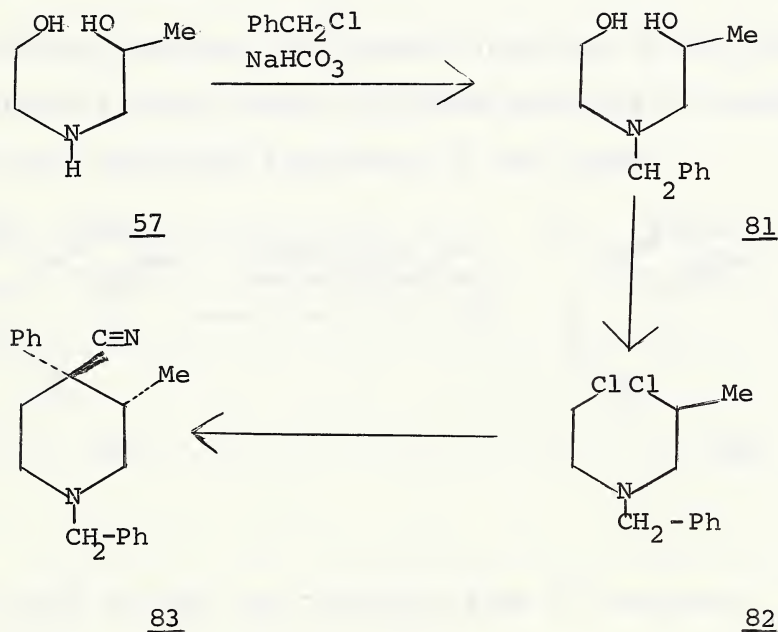


is protonated. The structure of the amidine is further confirmed by its PMR characteristics (Hz from TMS in CDCl_3 at 60 MHz): 445 main peak of multiplet (5 aryl protons); 293 singlet (3 amine protons); 155-108 (10 protons due to N-methyl and piperidine ring protons) and 75.5 doublet (3 methyl protons); the 3 proton signal at 293 Hz shifted downfield when D_2O was added to the CDCl_3 solution.

The amidine (plus the two nitriles) also resulted when phenylacetonitrile (1 mole) was added slowly to sodamide (2 moles) and dichloro compound (75) (1 mole) in toluene followed by a 6 hr. reflux period. In this experiment, a new compound was isolated from the chloroform extract in a very small amount (approximately 100 mg) which melted at $191\text{--}193^\circ$. This compound was assigned the β -1,3-dimethyl-4-phenyl-4-piperidinoamidine structure (80) due to the appearance of C=N (1680 cm^{-1}) and N-H and NH_2 ($3380\text{--}3120\text{ cm}^{-1}$ region) bands in IR spectrum, elemental analyses (high nitrogen analysis rules out the possibility of amide) and the observation that β -isomers in general are higher

melting than the corresponding α -4-phenylpiperidine isomers.

2. N-Benzyl Route:

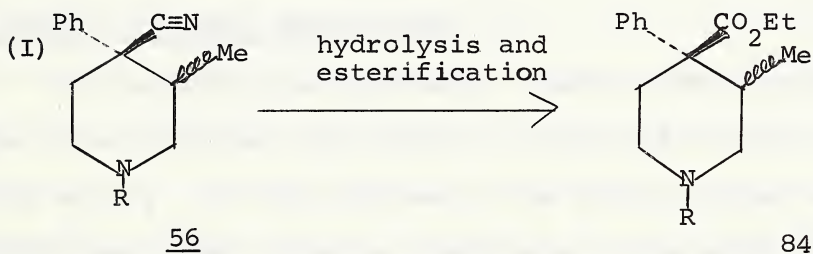


N-Benzyl-2-hydroxyethyl-2-hydroxypropylamine (81) was prepared from N- β -hydroxyethyl-N- β -hydroxypropylamine (57) and benzyl chloride in $\text{NaHCO}_3\text{-H}_2\text{O}$ according to a general N-alkylation procedure (Willson and Wheeler 1941). N-Benzyl-2-chloroethyl-2-chloropropylamine (82) was obtained as usual from the corresponding diol (81) and thionyl chloride, and purified by distillation. When this dichloro compound (82) was condensed with phenylacetone nitrile using sodamide as a condensing agent, only one isomer could be obtained in a pure form. This isomer was assigned the β -

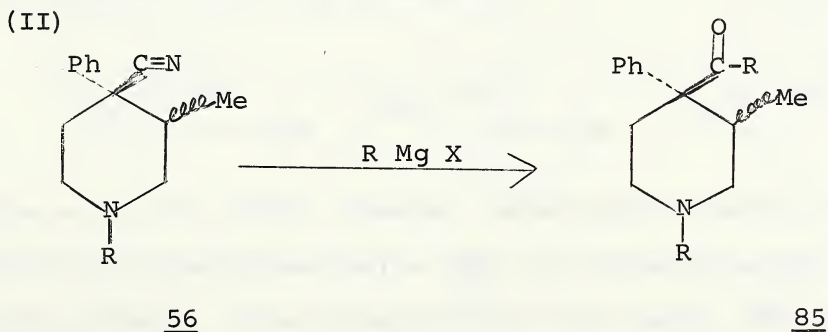
(cis 3-Me/4-Ph) configuration (83) on the basis of PMR data and its chemical correlation with the corresponding β -N-methyl and β -N-p-tosyl compounds (see later).

CONVERSIONS OF DIASTEREOISOMERIC NITRILES INTO POTENTIALLY ACTIVE ANALGESICS:-

Having obtained the isomeric nitriles in both the N-methyl and N-tosyl series, the next step was to convert these into potential analgesics of two types:

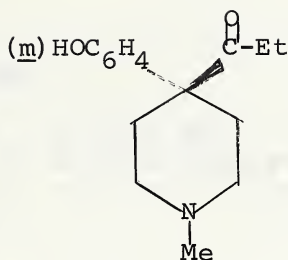


This would provide the pethidine type of analgesic.



These compounds would be close analogues of keto-bemidone (86).

These conversions were initially investigated using

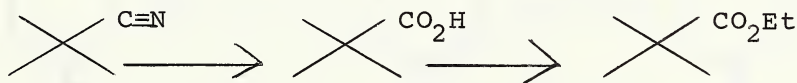


86

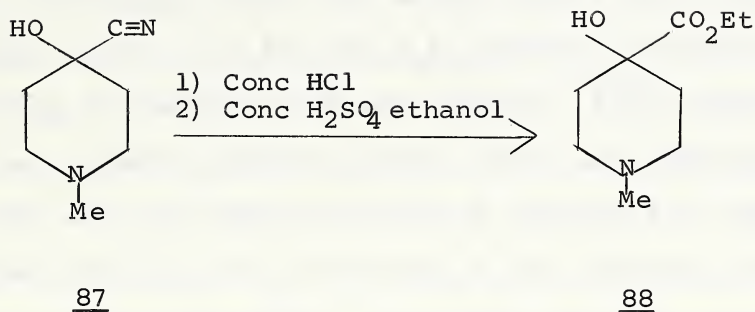
the N-methyl derivatives (76) which were available before the N-tosyl analogues.

4-ETHOXY CARBONYL DERIVATIVES:-

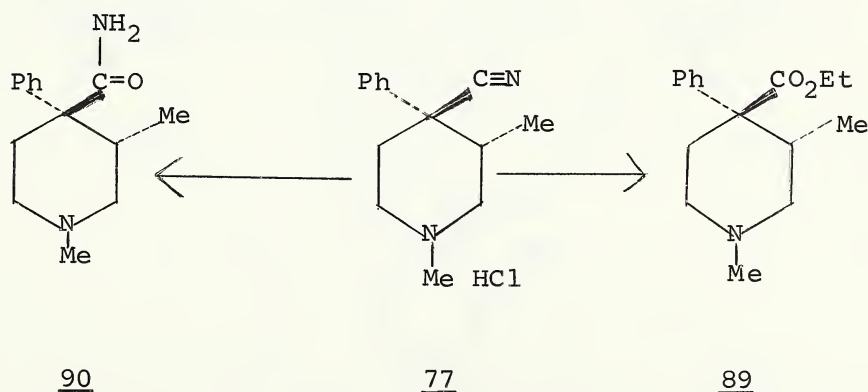
In the pethidine synthesis, Eisleb (1941) noticed that the hydrolysis of nitrile to acid did not go to completion easily. In his synthesis, the nitrile group was first hydrolyzed under vigorous conditions to the acid (KOH-MeOH or dil H_2SO_4) which was then, with or without isolation, converted to the corresponding ethyl ester either by $\text{SOCl}_2\text{-EtOH}$ or $\text{EtOH-H}_2\text{SO}_4$ method.



Lyle and Lyle (1954), however, esterified N-methyl-4-hydroxy-4-piperidinonitrile (87) by concentrated HCl -conc. H_2SO_4 -ethanol. The corresponding ethyl ester (88) was obtained in 70% yield. Therefore, in the first attempt, conc. HCl followed by H_2SO_4 -ethanol according to the procedure of Lyle and Lyle (1954) was used to esterify β -1, 3-dimethyl-4-phenyl-4-piperidinonitrile (77) hydrochloride.



This resulted in a basic mixture, the IR spectrum of which displayed bands characteristic of the starting material ($\nu_{\text{C}\equiv\text{N}}$ 2210 cm^{-1}), the ester (89) ($\nu_{\text{C}=\text{O}}$ 1710 cm^{-1}) and the amide (90) ($\nu_{\text{C}=\text{O}}$ 1670 cm^{-1}); the intensity of the latter band showed the amide to be the major component. The pure amide separated from a solution of the mixture in benzene as a solid m.p. 160-161°. This material was con-

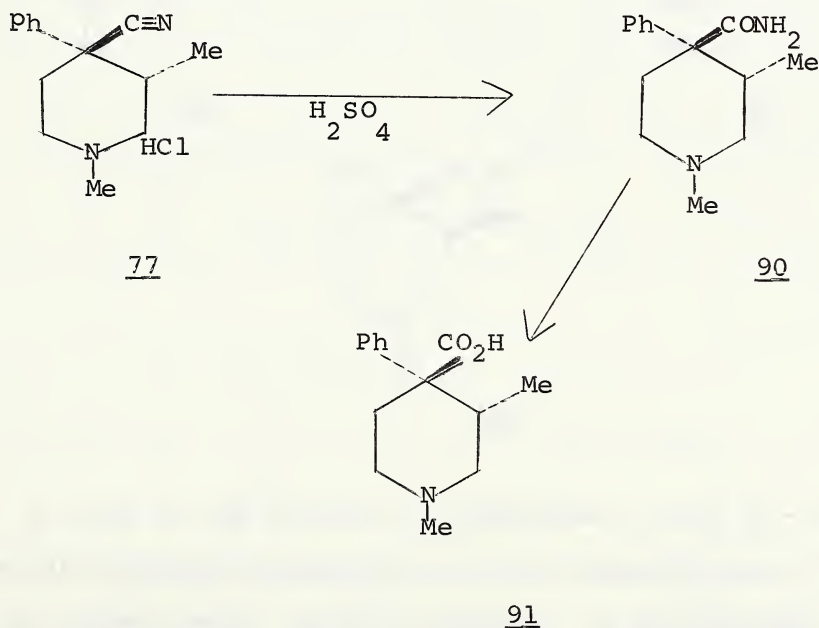


firmed to be β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamide (90) by IR data (ν_{max} 1670 cm^{-1} and NH_2 bands) and elemental analyses.

Since the nitrile group of (77) proved to be resis-

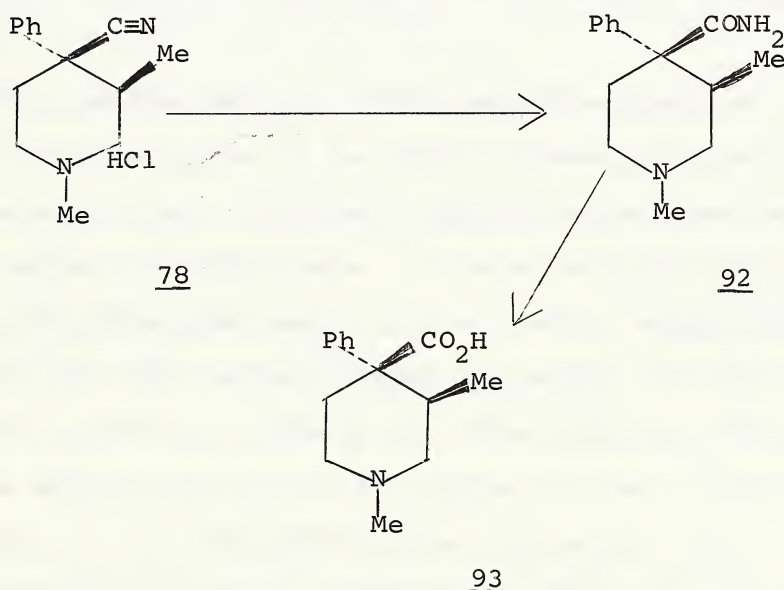
tant to hydrolysis beyond the amide stage a more vigorous procedure using the H_2SO_4 and H_2SO_4 -ethanol (based on a method due to Diamond 1957) was applied. Again amide (90) was the main reaction product which was separated in a pure form and its identity proved by identical IR spectra and mixed melting point with that of the authentic sample.

In a third experiment, an attempt was made to isolate the amino acid itself. The β -nitrile (77) was heated under reflux with conc. H_2SO_4 and a small amount of water until a test portion, diluted with water, failed to yield a precipitate with NaOH solution. The reaction product was then processed to give amide (90) as a minor product



and a high melting point salt as a major product. This salt gave a positive test for Cl^- and SO_4^{2-} ions and ap-

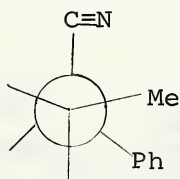
peared to be a mixed salt (i.e. Hydrochloride-hydrogen-sulphate) of the carboxylic acid (91) ($\nu_{\text{max.}}$ 3300-3150 ($-\text{C}-\text{OH}$) and 1670 ($-\text{C}-\text{OH}$) cm^{-1}). Carbon and hydrogen analyses correspond with the sulphate but not the nitrogen analysis. Similar hydrolysis of α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (78) HCl resulted in two compounds which were probably the corresponding amide (92) and carboxylic acid (93) but attempts at purifying these compounds by recrystallization failed.



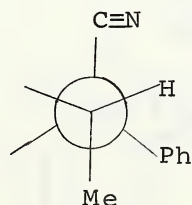
In view of the failure to hydrolyze α - and β -1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochlorides (78 and 77 respectively) by acid reagents, it was decided to attempt base hydrolysis using potassium hydroxide. When β -1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (77) was heated under reflux with KOH-ethylene glycol, the

corresponding amide was again obtained in major yield. A similar attempt to hydrolyze the corresponding α -isomer (78) resulted in a basic mixture judged from its IR spectrum to be composed of a nitrile as minor and amide as a major constituent. No pure products could be isolated. The β -amide (90) was also recovered after treatment with 30% NaOH at the reflux temperature, while various attempts to convert the α -amidine to the corresponding acid and/or amide were unsuccessful (amidines are generally readily hydrolyzed) (Shriner and Newmann 1944).

The cyanide function in the pethidine precursor is highly hindered since it is axially placed group adjacent to the bulky phenyl group and vigorous methods are required to effect its hydrolysis. It is evident from the present hydrolysis experiments that a 3-methyl substituent in (77) and (78) further hinders the attack of hydrolytic reagents upon the nitrile group. The hindrance offered by the methyl group should be greater in the α -derivative (because of the 3-Me/4-C \equiv N gauche interaction) than in the corresponding β -isomer (3-Me/4-C \equiv N) being trans in this case.



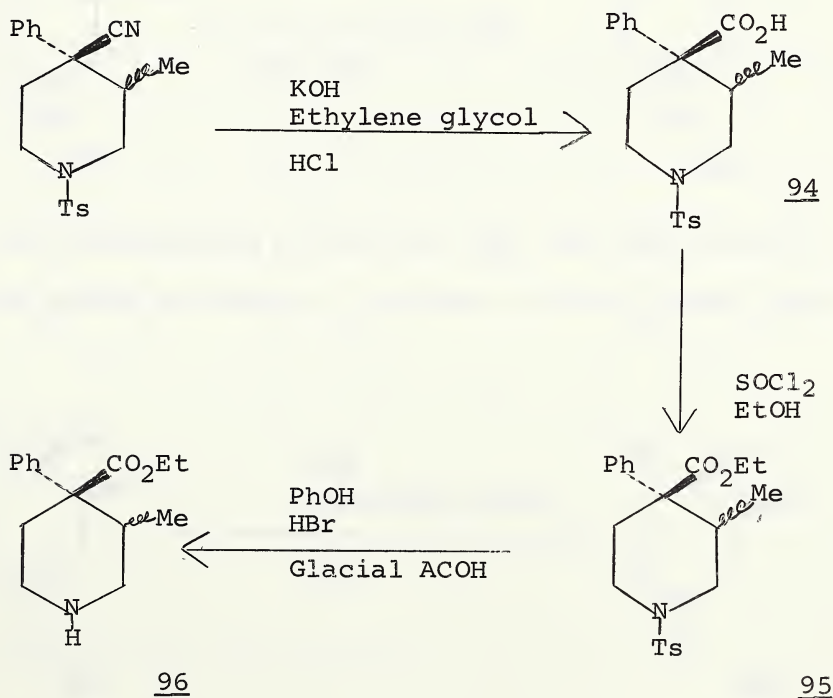
Newman's projection of C₃ and C₄ atoms in α -isomer.

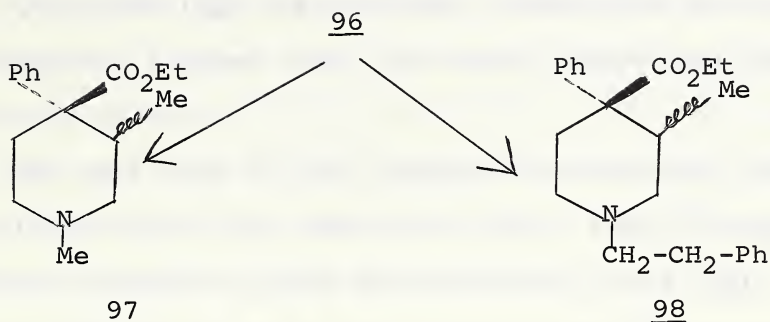


Newman's projection of C₃ and C₄ atoms in β -isomer.

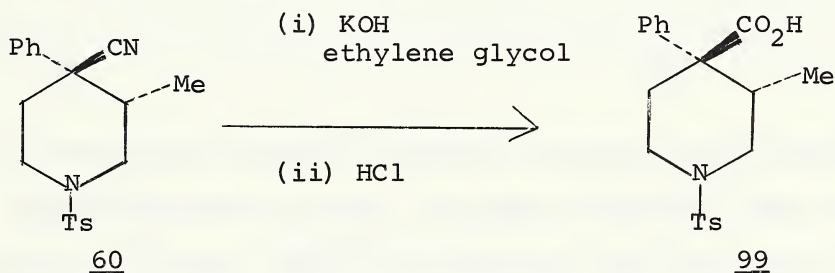
The β -isomer, in fact, provided more amide than the corresponding α -isomer under comparable hydrolytic reaction conditions.

In view of the difficulties met in hydrolyzing the N-methyl nitriles, attention was next directed to the N-tosyl analogues which had become available in the interim. The patent procedure (Janssen 1963) for the hydrolysis of these nitriles appeared straightforward and no difficulties were mentioned. The N-tosyl acids (94), in contrast with the N-methyl analogues, are insoluble in aqueous acid and hence their isolation and purification is far easier to achieve. The following sequence of reactions was carried out:-

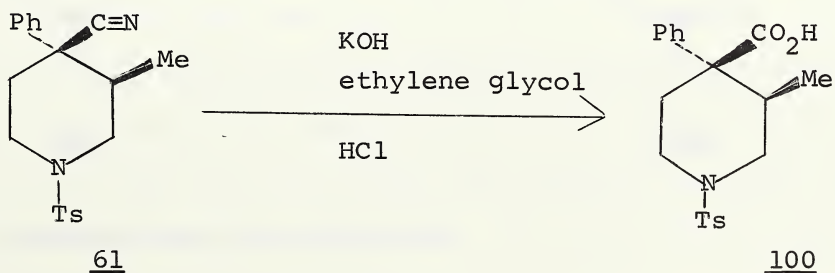




When the β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (60) was heated with KOH-ethylene glycol at 170° for 9 hr, acidification of the product gave the corresponding carboxylic acid (99) in excellent yield; its melting point was close to that reported by Janssen (1963).

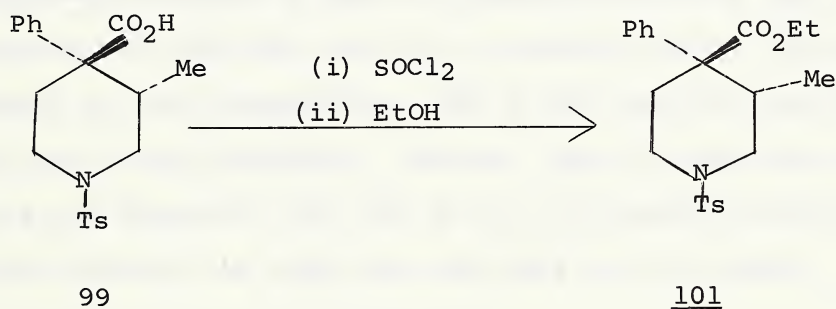


When the corresponding α -nitrile (61) was hydrolyzed by the same patent procedure, a mixture of the α -acid (100)

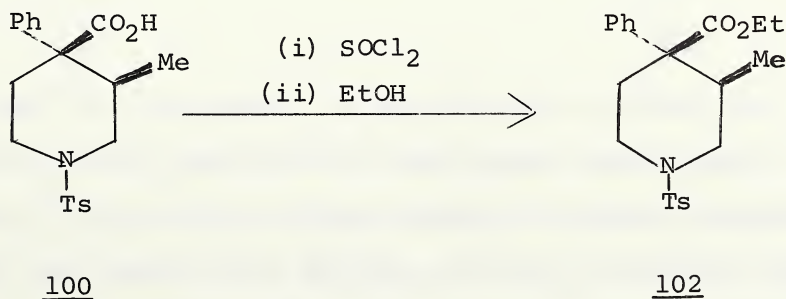


and α -cyanide (61) was obtained. Hydrolysis was essentially complete, however, when the reflux period was increased from 9 to 24 hr.

The next step in this sequence of reactions was the esterification of the carboxylic acid. When β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylic acid (99) was esterified by SOCl_2 -EtOH method according to Janssen's procedure (1963), the desired ester (101) was obtained.

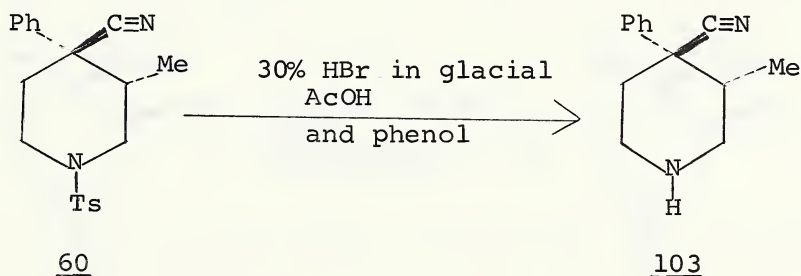


When α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylic acid (100) was treated under the same conditions, the corresponding α -ester (102) was similarly obtained which on recrystallization from methanol melted at $127-128^\circ$ (Janssen

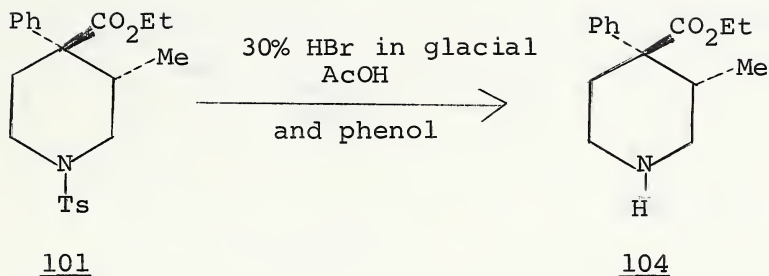


1961 reported m.p. $127.8-128.2^\circ$).

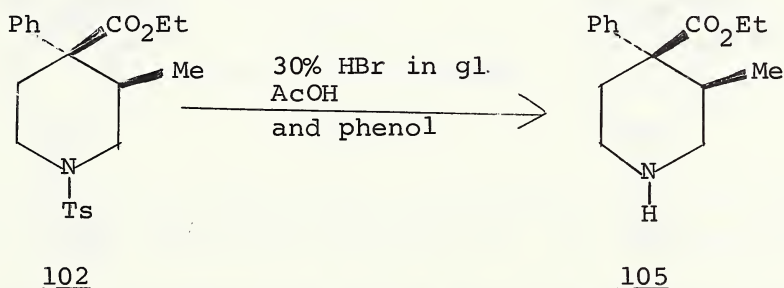
The third step in the reaction sequence was the removal of the N-tosyl group to give a secondary amine. In the patent description (Janssen 1963), detosylation is effected by cold 30% HBr solution in glacial acetic acid and phenol (phenol is used to avoid the bromination of the desired compound). This is a mild method of detosylation and is used to remove N-tosyl groups at room temperature without affecting other acid-labile substituents. When β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (60) was treated with 30% HBr solution in glacial acetic acid and phenol at room temperature, 82% of the starting material was recovered unchanged. However, when the reaction mixture was heated at 120° for 6 hr., β -3-methyl-4-phenyl-4-piperidinonitrile (103) was obtained in 52 % yield.



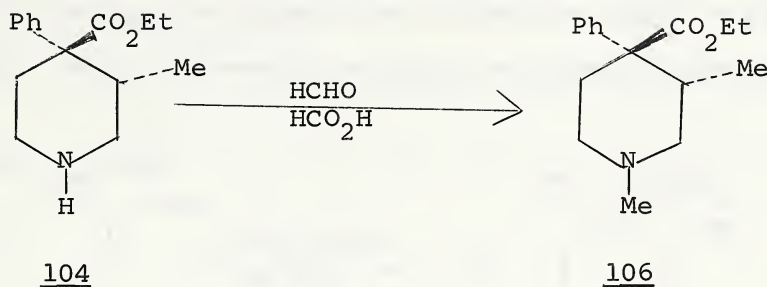
In view of this result, it was decided to carry out other N-detosylation reactions at the higher temperature. When ethyl β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylate (101) was heated with 30% HBr solution in glacial AcOH and phenol at 120° for 6 hr., the corresponding secondary amine (104) was obtained in 85% yield. The structure of this com-



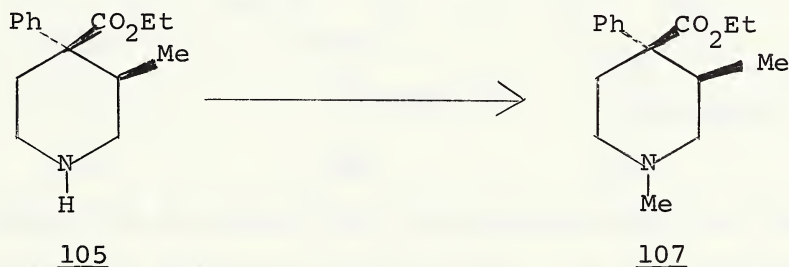
pound (104) was confirmed by the appearance of NH , $\text{--}\overset{\text{O}}{\parallel}\text{COEt}$ bands (3300 and 1730 cm^{-1} respectively) and the disappearance of $\text{--}\overset{\text{O}}{\parallel}\text{S=O}$ symmetrical and non-symmetrical stretching frequencies (1165 and 1350 cm^{-1} respectively) in the IR spectrum. Similarly, when ethyl α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylate (102) was treated in the same fashion, the corresponding detosylated compound (105) was obtained in about 80% yield.



The last step was to N-alkylate the secondary amino esters (104 and 105). When ethyl β -3-methyl-4-phenyl-4-piperidinocarboxylate (104) was N-methylated by a mixture of 37% formalin and 88% HCO_2H , the desired N-methyl compound (106) was obtained. This ester (106) formed a hydro-



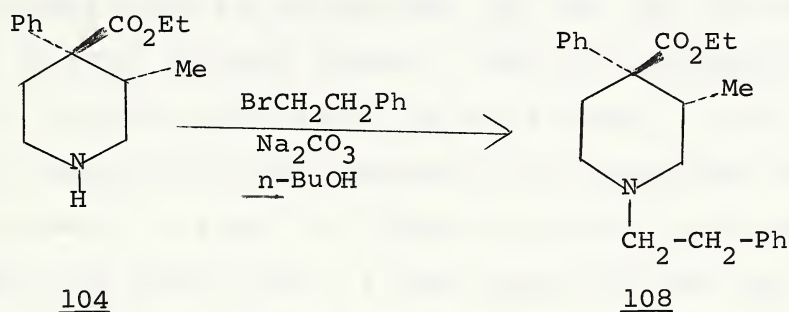
chloride corresponding in melting point with that of the reported material (Janssen 1963). This ester (106) was shown to be the β -(cis 3-Me/4-Ph) isomer on the basis of PMR data (see later). When ethyl α -3-methyl-4-phenyl-4-piperidinocarboxylate (105) was N-methylated under similar conditions, an N-methyl ester (107) hydrochloride was obtained. This compound was shown to have the α -(trans



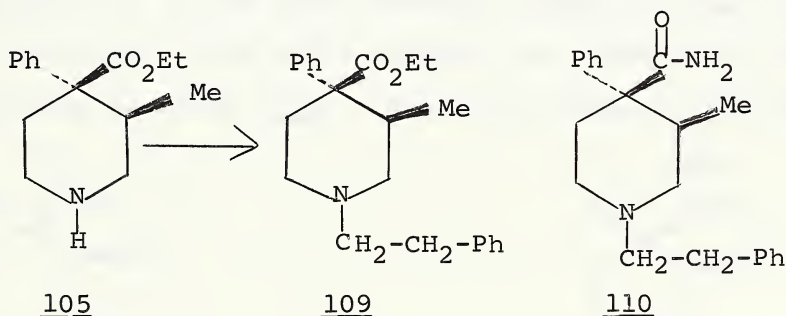
3-Me/4-Ph) configuration on the basis of PMR data (see later).

Finally, the N-phenethyl esters (108) and (109) were prepared. When ethyl β -3-methyl-4-phenyl-4-piperidinocarboxylate (104) was allowed to react with 2-bromoethylbenzene in the presence of Na₂CO₃ using n-butanol as a solvent ac-

cording to Elpern's procedure (1957), ethyl β -N-phenethyl-3-methyl-4-phenyl-4-piperidinocarboxylate (108) was obtained. Ethyl α -3-methyl-4-phenyl-4-piperidinocarboxylate



(105) was similarly converted to the corresponding N-phenethyl analogue (109). This compound (109) formed a

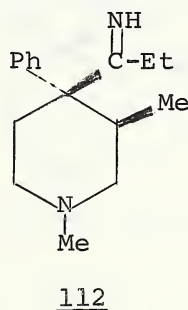
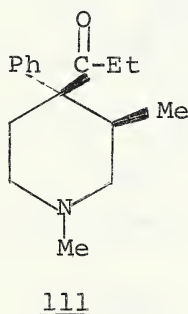


hydrochloride in ether which on recrystallization from ethanol-ether melted at 176.5-177.5°. In one experiment, however, an attempt to prepare the α -N-phenethyl ester (109) hydrochloride from the corresponding crude secondary amine, resulted in a new compound (m.p. 231-235°) which was assigned α -N-phenethyl-3-methyl-4-phenyl-4-piperidinocarboxamide (110) on the basis of elemental analyses (the amide probably formed from the incompletely hydrolyzed nitrile

present in the mixture).

4-PROPIONYL DERIVATIVES:-

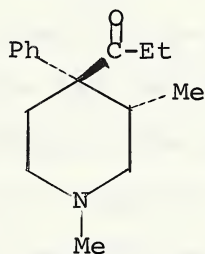
These ketones may be obtained from either the N-methyl or N-tosyl 4-nitrile derivatives (56) and (76) by reaction with an ethyl Grignard reagent. When α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (78) was allowed to react with ethyl magnesium bromide (prepared from bromoethane and magnesium metal in ether) in toluene according to the method of Nunn and Henze (1947), a dark brown oily base was obtained. The IR spectrum of this base showed no nitrile band but two bands (1700 and 1640 cm^{-1}) were present in the C=O/C=N region. The band at higher wave number (1700 cm^{-1}) is indicative of the ethyl carbonyl group of (111) while the lower band (1640 cm^{-1}) suggest the presence of the corresponding ketimine (112). Reaction between a cyanide func-



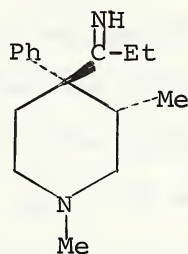
tion and a Grignard reagent is known to proceed via a ketimine and these intermediates are fairly stable in hindered situations (Hassan 1967). The IR characteristics of ketimines are well known (Pickard and Poly 1954, Hassan 1967); there are bands in the $1645\text{--}1639\text{ cm}^{-1}$ region ascri-

bed to C=N stretching and $\sqrt{\text{N-H}}$ bands in the 3247-3205 cm^{-1} region. Some ketimines related to methadone have been tested as analgesics and found to be less active than the corresponding ketones (Janssen and Jageneau 1957). In view of this, no special attempt was made to isolate the ketimine (112) in pure form. The mixture of ketone (111) and ketimine (112) was hydrolyzed with dilute hydrochloric acid to yield the ketone (111), which was purified by distillation. Attempts to prepare crystalline salts of this material (e.g. a hydrochloride, hydrobromide and oxalate) met with failure.

When β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (77) was treated with ethyl magnesium bromide under similar conditions, again a mixture of ketone (113) and ketimine (114) was obtained (IR evidence) and the pure ketone was



113

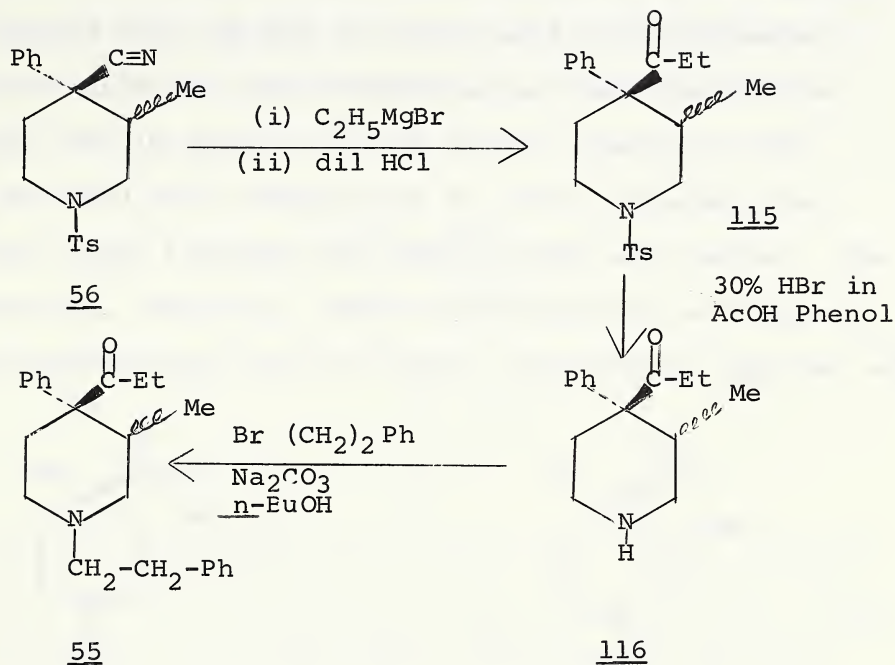


114

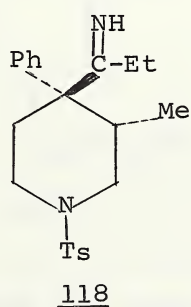
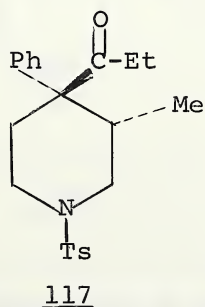
obtained as before by acid hydrolysis (the IR of the product has no ketimine band at 1625 cm^{-1} and a sharp $\sqrt{\text{C=O}}$ band at 1705 cm^{-1}). The β -ketone (113) formed a solid hydrochloride m.p. 238-242°.

In order to obtain ethyl N-phenethyl-3-methyl-4-phenyl-4-piperidinoketone diastereoisomers (55), the following

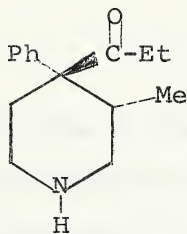
sequence of reactions was planned:-



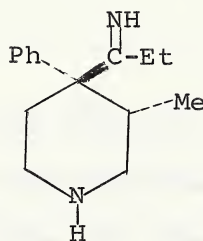
When β -N-p-tosyl-3-methyl-4-phenyl-4-piperidino-nitrile (**60**) was treated with ethyl magnesium bromide according to the same conditions used for the corresponding N-methyl compound, a mixture of ketone (**117**) and ketimine (**118**) was obtained. It was believed that any ketimine



would be converted to the corresponding ketone under detosylation conditions. With this in view, the above mixture was treated with 30% HBr in acetic acid in the presence of phenol using the same conditions as described before. However, the IR spectrum of the product (bands at 3300, 1705 and 1630 cm^{-1}) showed that it still contained some ketimine (120) although the carbonyl band was sharper. The mixture was, therefore, further hydrolyzed by heating with dilute hydrochloric acid to yield a pure ketone (119) and sub-

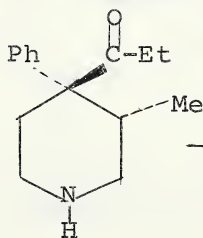


119

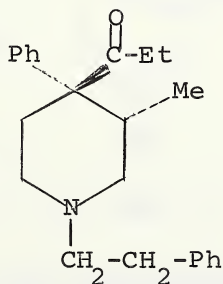


120

jected to N-phenethylation as before to yield ethyl β -N-phenethyl-3-methyl-4-phenyl-4-piperidinoketone (121).



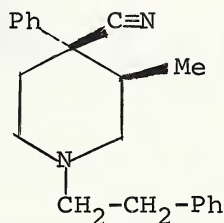
119



121

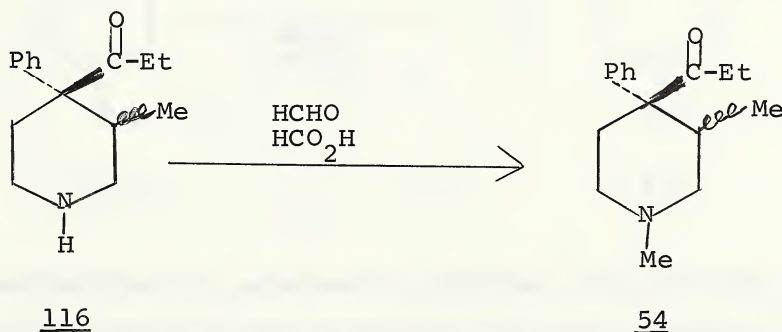
Treatment of the α -N-tosylcyanide (61) with ethyl magnesium bromide yielded a mixture of ketone, ketimine and

unchanged nitrile (IR evidence). The crude product after detosylation, acid hydrolysis ($\text{HCl-H}_2\text{O}$) and N-phenethylation resulted in a mixed nitrile-ketone hydrochloride from which only the nitrile compound (122) could be isolated in a pure form.



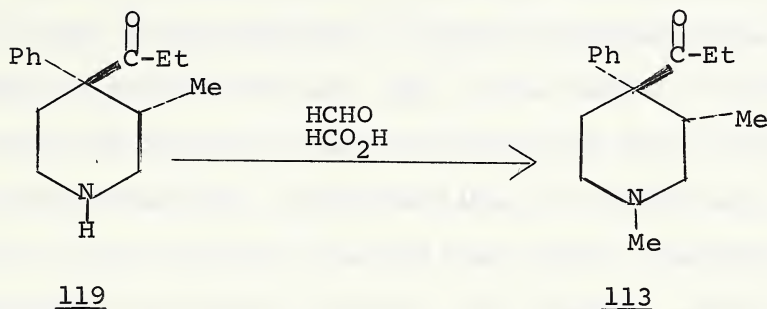
122

In view of the easy availability of ethyl α - and β -3-methyl-4-phenyl-4-piperidinoketone diastereoisomers (116), it was decided to convert these compounds into the corresponding N-methyl derivatives (54) using the $\text{HCHO-HCO}_2\text{H}$ method.

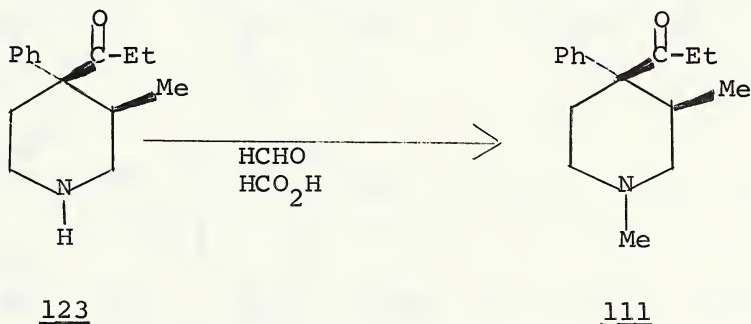


When ethyl β -3-methyl-4-phenyl-4-piperidinoketone (119) was N-methylated, the desired ethyl β -1,3-dimethyl-4-phenyl-4-piperidinoketone (113) was obtained which was found to be completely identical with the ketone previously

obtained from β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (77) by reaction with ethyl magnesium bromide (IR and mixed m.p. of the hydrochlorides evidence). Similarly when ethyl



α -3-methyl-4-phenyl-4-piperidinoketone (123) was N-methylated under comparable conditions, ethyl α -1,3-dimethyl-4-phenyl-4-piperidinoketone (111) resulted along with traces of the corresponding nitrile; the mixture was

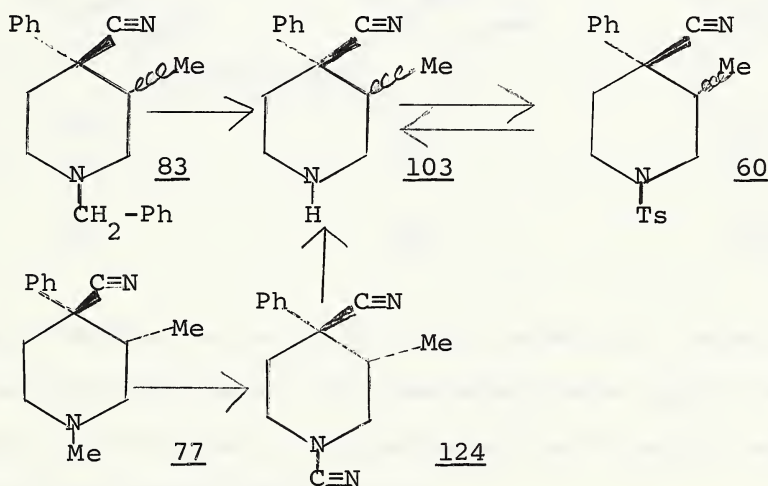


chromatographed on alumina to provide a pure ketone (111) fraction (obtained when benzene used as an eluant). This ketone was identical with the ethyl α -1,3-dimethyl-4-phenyl-4-piperidinoketone obtained from the corresponding nitrile (78). On this evidence, ethyl α -1,3-dimethyl-4-phenyl-4-piperidinoketone obtained from the N-tosyl route and all its precursors were unequivocally confirmed to have

the trans (3-Me/4-Ph) configuration.

CHEMICAL CORRELATIONS BETWEEN N-METHYL, N-BENZYL AND N-TOSYL ISOMERS OF 3-METHYL-4-PHENYL-4-PIPERIDINONITRILES:-

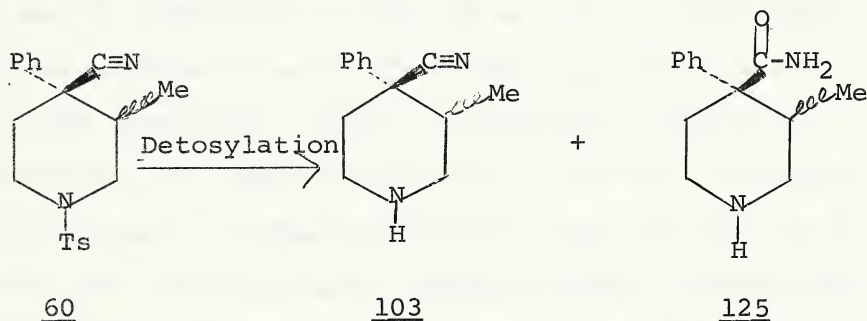
It was found possible to assign configurations to the isomeric N-methyl nitriles (76) on the basis of differences in their PMR spectral characteristics and this evidence is discussed separately. Configurations of the N-tosyl isomers and the single N-benzyl derivatives could, therefore, be established by relating them to the N-methyl isomers. The correlation scheme is shown below:-



When N-benzyl-3-methyl-4-phenyl-4-piperidinonitrile (83) hydrochloride (m.p. 235.5-236.5°) was treated with palladized carbon and hydrogen gas in 95% ethanol at room temperature, 3-methyl-4-phenyl-4-piperidinonitrile (103) hydrochloride was obtained. N-Tosylation of this secondary base (103) by the p-tosyl chloride -Na₂CO₃ method gave an

N-tosyl derivative (60) which was identical with the β -tosyl isomer obtained by the cyclization procedure (originally it was planned to use the N-tosyl derivative (60) as a seed material to aid isomer separation in the cyclization reaction. Eventually, this did not prove to be necessary).

When β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (60) was detosylated by 30% HBr in AcOH and phenol, by heating to reflux for 4 hr., the desired secondary amine (103) and the corresponding amide m.p. 191-192° (125)



were obtained as major and minor products, respectively. The hydrochloride of this secondary base (103) was identical with the salt obtained when the N-benzyl isomer (83) was reductively debenzylated.

The final step in these correlations was to convert the β -N-methyl nitrile (77) to the corresponding secondary base by means of a Von Braun demethylation reaction using cyanogen bromide. When β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (77) was heated under reflux with cyanogen bromide in chloroform with stirring, β -N-cyano-3-methyl-4-phenyl-4-piperidinonitrile (124) was obtained as

a non-basic reaction product. Its IR spectrum showed an intense absorption band at 2200 cm^{-1} (typical of $\text{N-C}\equiv\text{N}$ stretching; Casy and Hassan 1967); the $\text{C-C}\equiv\text{N}$ band of the precursor (also near 2200 cm^{-1}) being very weak. No attempt was made to isolate the quaternary salt (methbromide) formed as by product in these reactions. When β -N-cyano-3-methyl-4-phenyl-4-piperidinonitrile was heated under reflux with dilute hydrochloric acid, the corresponding secondary amine (103) was obtained. The hydrochloride of this amine was identical (by mixed melting point and IR comparisons) with the secondary amine hydrochlorides obtained from the β -N-tosyl (60) and the N-benzyl (83) compounds. Hence 1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (m.p. $275\text{-}276^\circ$), N-benzyl-3-methyl-4-phenyl-4-piperidinonitrile hydrochloride (m.p. $235.5\text{-}236.5^\circ$) and N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (m.p. $217\text{-}218^\circ$) were assigned identical configurations and stand confirmed as β -(cis 3-Me/4-Ph) isomers. Therefore, the second N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile isomer (m.p. $149\text{-}149.5^\circ$) has the α -(trans 3-Me/4-Ph) configuration.

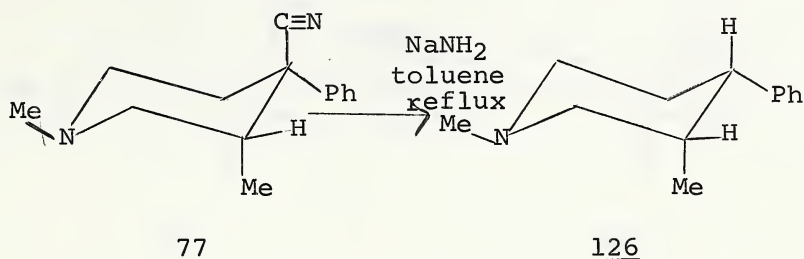
ATTEMPTED CONVERSION OF α 1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOAMIDINE (79) TO COMPOUND(S) OF KNOWN STEREOCHEMISTRY AND/OR VICE-VERSA:-

When N-methyl-2-chloroethyl-2-chloropropylamine (75) is cyclized with phenylacetonitrile in toluene using sodamide as a condensing agent, in addition to the two desired

diastereoisomeric nitriles (77 and 78), two corresponding amidine isomers (79 and 80) were obtained as by-products (discussed earlier). Stereochemical assignments to the amidines were tentatively made on the basis of their melting points (higher melting isomer was assigned the β - and lower melting the α -isomer). As the amidines are generally characterized by their relative ease of hydrolysis (Shriner and Newmann 1944), it was intended to hydrolyze these amidines to the corresponding amides or carboxylic acids which could subsequently be correlated with the compounds, of established stereochemistry. However, when the α -1,3-dimethyl-4-phenyl-4-piperidinoamidine (79) was subjected to hydrolysis using dilute hydrochloric acid, concentrated hydrochloric acid or alcoholic potassium hydroxide, the starting material was recovered in each instance. Unfortunately, availability of only a small quantity of β -1,3-dimethyl-4-phenyl-4-piperidinoamidine (which is probably more easily hydrolyzed than the corresponding α -isomer) precluded any attempt at hydrolysis.

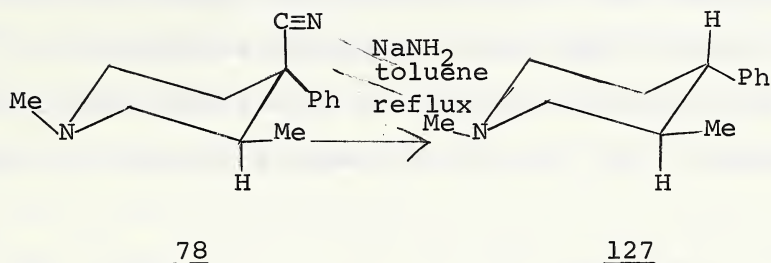
It is believed that amidines are obtained when excess of sodamide is present and the reaction period is prolonged. Therefore, a deliberate attempt was made to obtain the amidines by treating the nitrile compounds with sodamide in toluene under various conditions. When α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (78) was stirred at room temperature with sodamide and toluene for 48 hr., the starting material was recovered. However, when β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (77) was heated under reflux

with sodamide in toluene for 8 hr., a new compound was obtained. The IR spectrum of this compound showed no nitrile



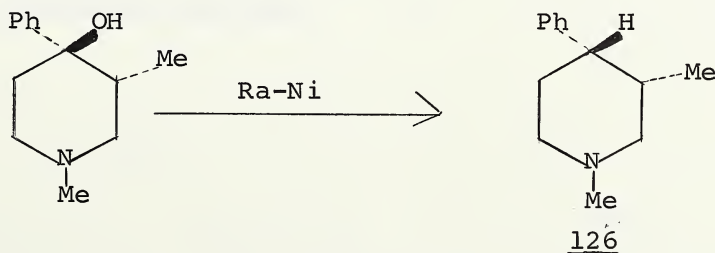
band (2210 cm^{-1}) but no band appeared at 1640 cm^{-1} ($\nu_{\text{C}=\text{N}}$) characteristic of an amidine. This material was assigned the structure β -1,3-dimethyl-4-phenylpiperidine (126) by comparison with an authentic sample prepared by a different route (see later). Sodamide (a strong base) is known to attack the cyano group when solvents such as benzene, toluene or xylene are used at the boiling point. Under such conditions, the nitrile function is eliminated as sodium cyanamide (Bergel 1944; Jackman 1949; and Ruddy 1951). Similarly, when α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (78) was heated to reflux with sodamide in toluene, a novel compound was obtained. The IR spectrum showed the elimination of the nitrile function (2210 cm^{-1} band absent) and again no band attributable to the amidine structure appeared at 1640 cm^{-1} . Therefore, this material was believed to be α -1,3-dimethyl-4-phenylpiperidine (127). This compound formed a crystalline hydrochloride (m.p. $232-235^\circ$) and methiodide (softens at $143-146^\circ$). The PMR data on the salts indicates that the α -isomer (127), is in fact a mix-

ture and contains a small amount of inversion product (see later).

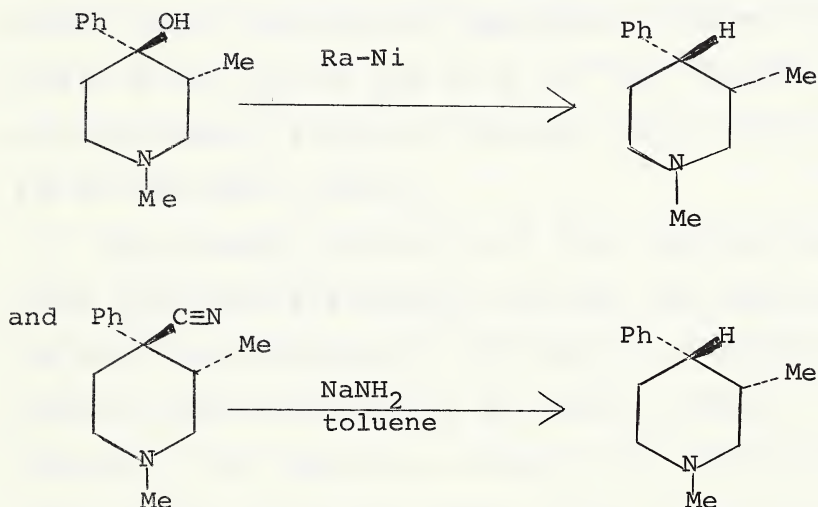


At this stage, amidine formation was considered to be the intermediate step in the elimination of the nitrile group by sodamide in boiling toluene. α -1,3-Dimethyl-4-phenyl-4-piperidinoamidine (m.p. 137-138°) was, therefore, subjected to sodamide and toluene treatment with the expectation of obtaining the corresponding α -1,3-dimethyl-4-phenylpiperidine (127); the starting material was, however, recovered.

β -1,3-Dimethyl-4-phenylpiperidine (126) has been previously synthesized independently (Casy and McErlane, unpublished results) by the Raney-Nickel hydrogenolysis of β -prodinol. The derived hydrochloride was identical with the compound obtained via the nitrile route (IR and mixed



m.p. evidence). However, no α -1,3-dimethyl-4-phenylpiperidine (127) could be obtained from the corresponding α -prodinol by Raney -Ni hydrogenolysis. The identity of β -1,3-dimethyl-4-phenylpiperidine (126) obtained from the prodine series with the compound obtained from β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (77), (assuming the



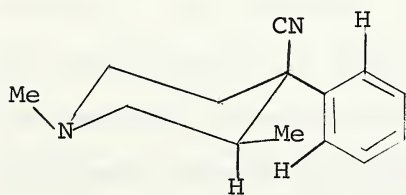
the above reactions to be stereospecific) correlates the stereochemistry of the nitrile compounds with the prodines and prodinols which in turn have been firmly established on the basis of X-ray crystallographic and PMR data (discussed earlier).

CONFIGURATIONAL ESTABLISHMENT OF SOME DIASTEREOMERS BY
PMR SPECTROSCOPY:

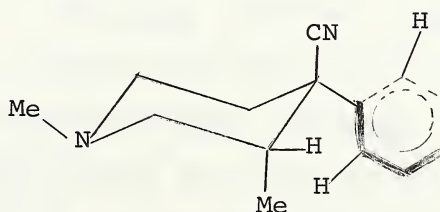
1. 1,3-Dimethyl-4-Phenyl-4-Piperidinonitrile Isomers

It has been noticed that the alkylation of phenyl acetonitrile with N-methyl-2-chloroethyl-2-chloropropylamine (75) resulted in two isomeric nitriles; this fact was also evident from the PMR spectrum of the total basic alkylation product which displayed two sec-methyl doublets (chemical shifts 48 Hz ($J=6$ Hz) and 45 Hz ($J=7$ Hz) from TMS in CDCl_3) and two N-methyl singlets (chemical shifts 141 Hz and 138 Hz from TMS in CDCl_3).

The isomeric nitriles have been separated and purified (discussed previously) and their PMR spectra studied. The PMR characteristics of α - and β -1,3-dimethyl-4-phenyl-4-piperidinonitriles are shown in Table V. Differences in the spectra are shown to be consistent with the α -isomer having the trans (3-Me/4-Ph) configuration, and the β -isomer, the cis (3-Me/4-Ph) configuration and support structures (128) and (129) as the most probable



128



129

conformations, respectively, of the two isomers (these conformers differ in the configuration of the 3-methyl group

and the relative orientation of the 4-phenyl group and the piperidine ring). The same reasons have been used as advanced by Casy (1966) for assigning the configurations to cis and trans 1-alkyl (and 1-arylalkyl)-4-aryl-3-methyl-piperidin-4-ols.

The 4-Phenyl signal:

In (128) the preferred orientation of the 4-phenyl group will be a plane approximately at right angles to that of the piperidine ring, the equatorial 3-methyl/or the aromatic hydrogen interaction being minimum in this conformation (cf. Allinger, et. al. 1962). In (129), however, the same orientation is not favoured since it would bring aromatic hydrogen in close proximity to an axial methyl group and the preferred orientation of the 4-phenyl group will be when it is approximately coplanar with the piperidine ring. Averaged environments will be experienced by all protons as a result of rapid rotation about the bond linking the two rings. In both isomers, however, it is considered that the populations of conformers akin to (128) and (129) will be higher than all others at any one time. In the trans conformers (128), the environments of ortho aromatic hydrogens should differ markedly from the corresponding meta and para hydrogens because the ortho-protons are close to the electronegative cyano group in the preferred conformation (128) and the equivalent form in which the ortho protons of (128) are interchanged. In the cis conformer (129), the ortho protons are further removed from the cyano

group and hence their chemical shift will be closer to those of the other aryl hydrogens. Hence chemical shift differences among the aromatic protons are expected to be more pronounced in the trans isomer with the result that the trans aromatic signal should be more complex than that of the corresponding cis isomer. This conclusion is confirmed experimentally; the aromatic signal of the α -isomer being markedly broader (WH6) than the corresponding β -signal (*WH2.5) (Fig. 1). The same effect was observed for the α'/β aryl signals of the prodinol isomer (Casy 1966). (*WH signifies width at half height).

The 3-Methyl Signal:

a) Chemical Shift: When the 4-phenyl group adopts a near perpendicular orientation with respect to the plane of the piperidine ring (as in 128), the equatorial 3-methyl substituent is judged to fall just within the diamagnetic screening zone of the benzene nucleus, while the axial 3-methyl group falls just within the same zone when phenyl is oriented as in (129) (these conclusions were reached by study of Dreiding models and application of the Johnson-Bovey (1958) screening data for benzene). Hence 3-methyl substituents should be screened in similar degree from the applied magnetic field in both isomers. In fact, the 3-methyl signals of the two isomers are up-field relative to those of 3-methyl in cyclic analogues in which a phenyl group is not adjacent to methyl (c.f. 76 and 130). However, the β -3-methyl signal was slightly

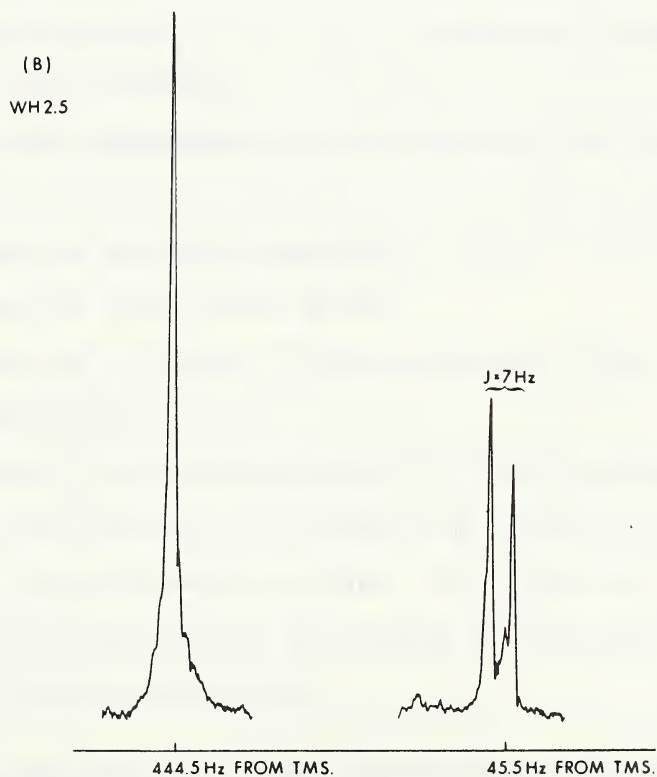
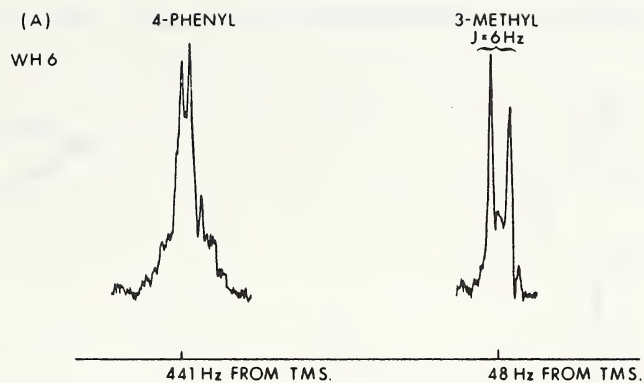
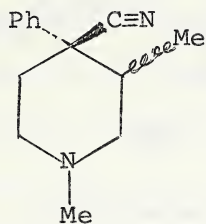
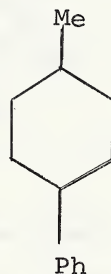


Fig. 1. Part of the PMR spectra of α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (A) and of the corresponding β -nitrile (B). Recorded on a Varian A-60 instrument in CDCl_3 .

higher field (3 Hz) than the corresponding α -signal. Var-



76



130

α 48 Hz (in CDCl_3)

60.5 Hz (in CDCl_3)

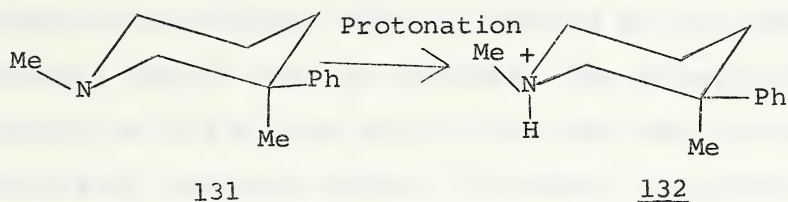
β 45.5 Hz (in CDCl_3)

ious factors may contribute to this chemical shift difference:-

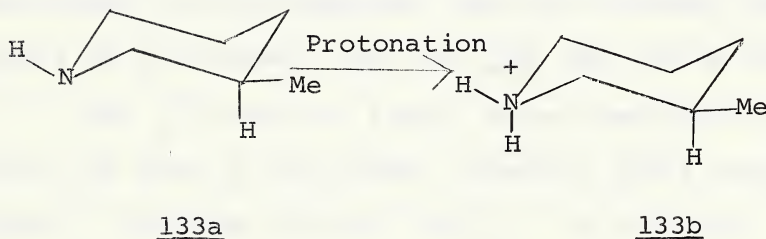
- 1.) influence of nitrogen lone pair.
- 2.) influence of the nitrile group.
- 3.) influence of C-C bonds of the piperidine ring
(Jackmann 1962).

These influences would be expected to differ in their effects upon the magnetic environment of axially and equatorially placed 3-methyl groups. No attempt is made here to analyze them further on account of the small chemical shift difference involved.

b) Effect of Protonation of the Basic Centre: The influence of proton uptake at a basic centre two carbons removed from a methyl group upon the methyl chemical shift is well demonstrated by the following examples. When 1-benzyl-3-methyl-3-phenylpiperidine (131) in CDCl_3 is protonated the 3-methyl resonance (a singlet) moves downfield by 25 Hz

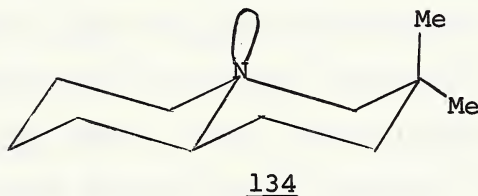


(Casy, unpublished results). There is little doubt that 3-methyl is axially oriented in the preferred conformation (131) of this compound. Hence, it will be in close proximity (bearing a 1,3-diaxial relationship) to the N-H^+ proton in the conjugate acid. However, when 3-methylpiperidine (133a) is protonated, there is a smaller difference (8 Hz) in the chemical shifts of 3-methyl group in the free base and the corresponding hydrochloride (133b).



Here the 3-methyl group is equatorially oriented in the preferred conformations (133a) and (133b). These results demonstrate the deshielding influence of protonated piperidinonitrogen upon the axial and equatorial 3-methyl groups. Its mechanism has not been established but results with the α -isomer (128), α -prodinol (Casy 1966) and 3-methylpiperidine (133a) etc. show that the inductive withdrawal of electrons by positively charged nitrogen

makes only a small contribution to deshielding; hence, magnetic anisotropic effects (induced by the positively charged centre) must be involved. The alternative explanation of the lone pair in the free base having a shielding influence whence its removal on protonation produces an apparent deshielding effect is unlikely since the lone pair has been shown to have a deshielding influence upon α -methyl in 3-methyl trans quinolizidines (134) (Moynihan et.al. 1962). With the above in mind,



α -Me downfield of e-Me signal by 16 Hz

the effect of N-protonation upon the 3-methyl chemical shift of the isomers (128 and 129) may now be considered.

The β -3-methyl signal moves downfield by 21.5 Hz when the base is protonated (chemical shift comparison made in the same solvent, CDCl_3). In contrast, the α -signal suffers a relatively small downfield shift (3.5 Hz). Of the two isomers, 3-methyl is further removed from the protonated basic centre in the α -conformer (128). Hence, β -3-methyl group must be axially and the corresponding α -group equatorially oriented. This is in agreement with the conformations and configurations (128) and (129) proposed for the α and β -isomers, respectively.

c) Multiplicity: While the 3-methyl signal of the β - isomer (129) (base in CDCl_3 and CCl_4) is a non-symmetrical doublet ($J=7$ Hz) that of the α -isomer is a narrower ($J=6$ Hz) non symmetrical doublet. Distortion of a methyl doublet is a typical result of virtual long range coupling (see below). As it occurs in both the isomers, no conclusions can be drawn regarding the orientation of the methyl substituent in the two isomers. It is, however, significant that virtual coupling effects are not observed in either isomer (128 and 129) hydrochloride. It may be argued that conditions for virtual coupling no longer obtain in 128 and 129 when a strong deshielding influence is introduced into the molecule which affects C-2 protons more than at C-3.

2. N-p-Tosyl-3-Methyl-4-Phenyl-4-Piperidinonitrile Isomers

The isomeric N-tosyl nitriles have very similar PMR characteristics. The only significant difference lies in the nature of the α - and β -3-methyl signals. Both have the same chemical shift but while the 3-methyl signal of the β -isomer (in CDCl_3) is a near symmetrical doublet ($J=7$ Hz) that of the α -isomer is a narrower ($J=6$ Hz) non-symmetrical doublet and shows evidence of a third peak. (Fig. 2). Distortion of a methyl doublet is a typical result of virtual long range coupling (Musher and Corey 1962) and its occurrence in the α rather than the β - isomer is interpreted in terms of (135) and (136) as

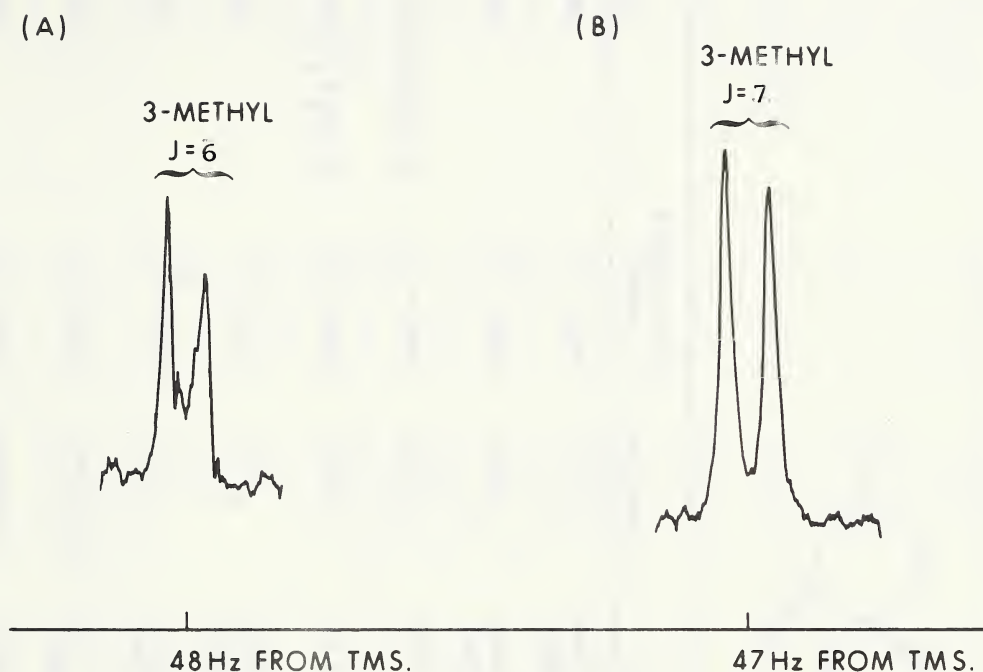
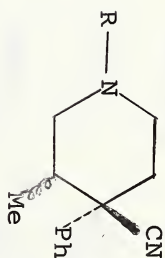


Fig. 2. Part of the PMR spectra of α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (A) and of the corresponding β -isomer (B). Recorded on a Varian A-60 instrument in CDCl_3 .

TABLE V. PMR CHARACTERISTICS OF SOME N-SUBSTITUTED-3-

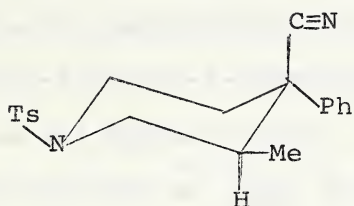
METHYL-4-PHENYL-4-PIPERIDINONITRILES



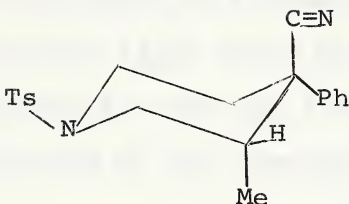
No.	R	Isomer and Form	Solvent	4-Ph	PMR Signals ^a	
					3-Me	Others
1.	Me	α -base	CDCl ₃	441 ^b (WH6)	48 ^c (J=6)	141 ^d (N-Me)
2.	Me	β -base	CDCl ₃	444.5 ^b (WH2.5)	45.5 ^c (J=7)	139.5 ^d (N-Me)
3.	SO ₂ C ₆ H ₄ Me-p	α -base	CDCl ₃	452 ^f	48 ^c (J=7)	
4.	SO ₂ C ₆ H ₄ Me-p	β -base	CDCl ₃	453 ^f	47 ^e (J=5.8)	
5.	Me	α -base	CCl ₄	452 ^b (WH6.5)	46 ^c (J=6)	138.5 ^d (N-Me)
6.	Me	β -base	CCl ₄	438.5 ^b (WH2)	43 ^c (J=7)	136 ^d (N-Me)
7.	Me	α -base	DMSO-d ₆	446 ^b (WH6)	40 ^e (J=6)	133.5 ^d (N-Me)
8.	Me	β -base	DMSO-d ₆	449 ^b (WH2.5)	36.5 ^e (J=7.5)	131.5 ^d (N-Me)

No.	R	Isomer and Form	Solvent	4-Ph	3-Me	Others
9.	CH ₂ -Ph	β -base	DMSO-d ₆	442 ^g	39 ^e (J=6.5)	212 ^d (N-CH ₂ Ph) —
10.	C≡N	β -	CDCl ₃	442 ^b (WH2)	49.5 ^e (J=7)	
11.	Me	α -HCl	CDCl ₃	443 ^b (WH6)	51 ^e (J=6)	176 ^j (N-Me)
12.	Me	β -HCl	CDCl ₃	440.5 ^b (WH2)	66 ^e (J=7)	176 ^d (N-Me)
13.	H	β -HCl	CDCl ₃	447 ^b (WH2)	60 ^e (J=7.5)	
14.	Me-	α -HCl	DMSO-d ₆	450 ^b (WH3)	43 ^c (J=6)	171 ^d (N-Me)
15.	Me	β -HCl	DMSO-d ₆	446 ^b (WH3)	49 ^e (J=7)	169 ^d (N-Me)
16.	CH ₂ Ph	β -HCl	DMSO-d ₆	451 ^g	48.5 ^e (J=7.5)	272 ^d (N-CH ₂ Ph) —
17.	Me	α -HCl	D ₂ O	446.5 ^b (WH3)	47 ^e (J=6.5)	177 ^d (N-Me)
18.	Me	β -HCl	D ₂ O	440.5 ^b (WH2)	42 ^e (J=7.5)	179 ^d (N-Me)

(a) chemical shifts in Hz from TMS, spectra being measured at a frequency of 60 MHz.
 (b) main peak(s) of multiplet. (c) non-symmetrical doublet. (d) singlet. (e) near symmetrical doublet. (f) includes N-SO₂-C₆H₄-Me signal. (g) includes N-CH₂-Ph signal. (h) quartet (J=7 Hz). (i) triplet (J=7 Hz). (j) doublet (J=5 Hz) due to spin-spin coupling with N-H proton. (k) CH₂Me signal overlaps over doublet of 3-Me signal.

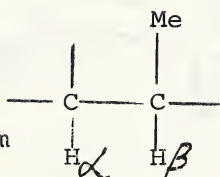


135



136

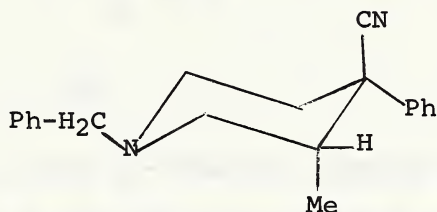
follows:



In the system H^α and H^β virtual coupling between methyl and H^α occurs when the coupling constant between H^β and H^α is large and of the same order as the chemical shift difference between the two protons. These conditions are more likely to prevail in (135) than in (136). α -isomer (135) contains an axial proton at C-3 which will be strongly coupled to the C-2 axial proton; (136) contains an equatorial proton at C-3 which is only weakly coupled to the methylene protons at C-2 ($J_{aa} > J_{ae} \approx J_{ee}$)

3. N-Benzyl-3-Methyl-4-Phenyl-4-Piperidinonitrile: In this series it is considered that a good evidence of configuration may be obtained even when only one isomer is available, by comparing the chemical shift values of 3-methyl in the base and base hydrochloride (Casy 1966). In the trans isomer, the two values should be similar, whereas in the cis, the salt value should be at a field strength significantly lower than that of the free base. When N-

benzyl-2-chloroethyl-2-chloropropylamine (82) was condensed with phenylacetonitrile, one isomer of N-benzyl-3-methyl-4-phenyl-4-piperidinonitrile (137) could be obtained as its hydrochloride. Evidence for the cis (3-Me/4-Ph) configuration of (137) was provided by the chemical shift



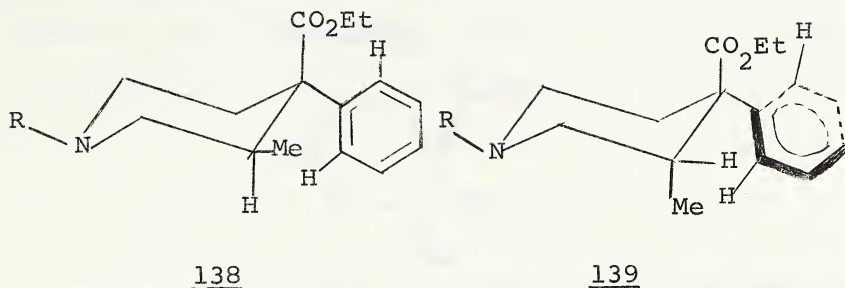
137

value of the salt (49 Hz) which was at a field strength significantly lower (10 Hz) than that of the free base (39 Hz) in DMSO- d_6 (this solvent was used because the salt was insoluble in $CDCl_3$). These values show close correspondence with those of 3-methyl (base and salt) in the β -1,3-dimethyl analogue examined in the same solvent (Table V). The β -(cis 3-Me/4-Ph) configuration of (137) was further confirmed by chemical correlations (discussed earlier).

Ethyl N-Substituted-3-Methyl-4-Phenyl-4-Piperidinocarboxylates:

The PMR characteristics (Table VI) of ethyl N-substituted-3-methyl-4-phenyl-4-piperidinocarboxylate isomers also provide evidence of configuration in $CDCl_3$ solution. The available PMR data are consistent with the α -isomer having the trans (3-Me/4-Ph) and β -isomer the

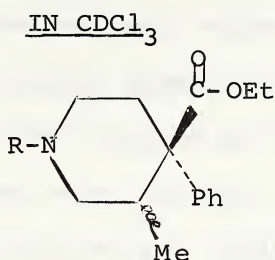
cis (3-Me/4-Ph) configuration.



The α and β -3-methyl signals of the esters (Table VI) differ in the same way as those in the corresponding nitriles (Table V) i.e. β -3-methyl signals are slightly higher field than the corresponding α -signals in the base form (probable factors responsible for this have already been outlined). The base to salt chemical shift difference in the β -isomers, in general, is found to be larger (10-17 Hz) than in the corresponding α -isomers (4-6 Hz). This data is consistent with data obtained previously on the corresponding isomeric nitriles (Table V) and piperidinols and their corresponding esters (Casy, 1966, 1968). The α -3-methyl group is deshielded by the presence of 4-carbethoxy group which is apparent from its unusually low chemical shift in the base (compare α -3-Me chemical shift of the corresponding nitrile in Table V). Little further deshielding is observed when the α -ester is protonated as expected (discussed earlier).

The PMR characteristics of the ethyl ester signals allow an additional differentiation to be made between isomers because of a difference in the positions of α and

TABLE VI. PMR CHARACTERISTICS OF SOME ETHYL N-SUBSTITUTED -3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATES



No.	R	Isomer and Form	PMR Signals ^a		
			3-Me	<u>CH₂-Me</u>	<u>CH₂-Me</u>
1.	Me	α -base	64 ^c	258 ^h	76 ⁱ
2.	Me	α -HCl	58 ^c	258 ^h	76 ⁱ
3.	Me	β -base	45 ^c	251 ^h	68 ⁱ
4.	Me	β -HCl	63 ^l	250 ^h	67 ^{i,k}
5.	(CH ₂) ₂ Ph	α -base	64	255	74 ^{i,k}
6.	(CH ₂) ₂ Ph	α -HCl	60 ^c	261 ^h	78 ⁱ
7.	(CH ₂) ₂ Ph	β -base	45	248 ^m	68 ^e
8.	(CH ₂) ₂ Ph	β -HCl	65 ^l	251 ^h	68 ^k
9.	SO ₂ C ₆ H ₄ Me	α -base	63 ^l	244 ^h	64 ^{i,k}
10.	SO ₂ C ₆ H ₄ Me	β -base	46 ^l	239 ^h	57 ^{i,k}

(l) 3-Me doublet overlaps over triplet of CH₂-Me signal.

(m) CH₂-Me signal duplicated. (n) CH₂Me signal overlap-

ped over N-Me signal. (o) CH₂-Me signal duplicated.

(p) CH₂Me signal duplicated.

N.B. Notations used here have the same meaning as described in the footnotes of Table V also.

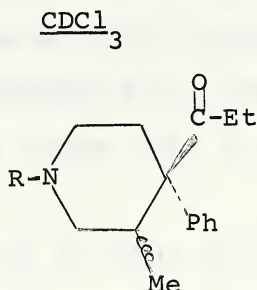
β - $\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{CH}_2-\text{Me}$ and $\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{CH}_2-\text{Me}$ signals (Casy 1968). The $\text{CO}_2\text{CH}_2-\text{Me}$ signals appear as triplets near 76 Hz in both α -N-methyl and α -N-phenethyl esters; in the corresponding β -isomers the signals appear at 67 and 68 Hz respectively (Table VI). The higher field values of the β -signals are consistent with the cis (3-Me/4-Ph) ester having a preferred conformation (139) because the ester group will spend some of its time above the plane of the phenyl group (i.e. well within the aromatic shielding zone). Similarly $-\text{CO}_2\text{CH}_2-\text{Me}$ signals appear as quartets near 258 Hz (255-261 Hz) in both α -N-methyl and α -N-phenethyl esters and near 250 Hz (247-251 Hz) in the corresponding β -signals. The higher field values of the cis signals are similarly interpreted in terms of the preferred conformation (139).

The PMR data available (Table VI, Nos. 9-10) on N-tosyl esters further demonstrate that the α -3-methyl group is deshielded by the ester grouping, a conclusion derived from comparison with the corresponding nitriles (Table V, Nos. 3-4). The $\text{CO}_2\text{CH}_2\text{Me}$ and $\text{CO}_2\text{CH}_2-\text{Me}$ signals of the N-tosyl esters differ in the same way as those in the N-methyl and N-phenethyl esters (described above), the former being quartets near 245 Hz (α) and 239 Hz (β) and the latter triplets near 64 Hz (α) and 57 Hz (β).

Ethyl N-Substituted-3-Methyl-4-Phenyl-4-Piperidinoketones:

The α - and β -3-methyl signals of the ketones differ in the same way as those in the corresponding nitriles

TABLE VII. PMR CHARACTERISTICS OF SOME N-SUBSTITUTED
-3-METHYL-4-PHENYL-4-PIPERIDINOETHYL KETONES IN



No.	R	Isomer and Form	3-Me	PMR Signals ^a	
				$\text{CH}_2\text{-Me}$	$\text{CH}_2\text{-Me}$
1.	Me	α -base	67 ^c	133 ⁿ	52 ⁱ
2.	Me	α -base in $\text{CDCl}_3\text{-CF}_3\text{CO}_2\text{H}$	66 ^l	132 ^h	59 ⁱ
3.	Me	β -base	42 ^l	139 ^h	52 ^k
4.	Me	β -HCl	60 ^e	134 ^h	54 ⁱ
5.	$(\text{CH}_2)_2\text{Ph}$	β -base	42 ^{e,1}	133 ^h	52 ^k
6.	$(\text{CH}_2)_2\text{Ph}$	β -HCl	61 ^l	133 ^h	53.5 ⁱ
7.	H	β -base	39 ^{e,1}	133 ^h	52 ^k
*8.	H	β -base in $\text{CDCl}_3\text{-CF}_2\text{CO}_2\text{H}$	43 ^l	133 ^h	53 ^k

N.B. Notations used here have the same meaning as described in the footnotes of Table V and VI.

*The small downfield shift of 3-Me in this case is probably due to solvation effects (discussed later).

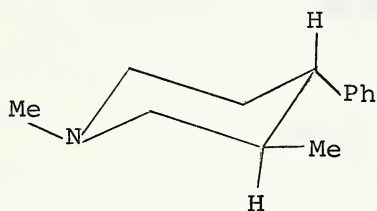
(Tables V and VII) the α -3 methyl signal (a deformed doublet 66 Hz) of the base appears at 65 Hz in the hydrochloride, corresponding values of the β -signal being 42 Hz (base) and 60 Hz (hydrochloride) i.e. β -base to salt chemical shift difference is larger than in the corresponding α -isomer.

The examination of Table VII shows that the chemical shift of the α -sec Me signal of the ketone base is lower field than the corresponding nitrile (Table V, Nos. 1 and 11) a result which must be due to the fact that the equatorial 3-Me group in the α -isomers falls in the deshielding zone of the carbonyl group. The α -3-Me chemical shift changes little on protonation as usual. The β -3-Me group is much less subject to carbonyl deshielding (cf. base value, Table VII, No. 3) in accord with its axial orientation. The $\underline{\text{CH}_2\text{Me}}$ and $\underline{\text{CH}_2\text{Me}}$ signals of the ketone are higher field than corresponding signals of the esters which are close to the strongly electronegative element, oxygen. Differences between α and β signals are not large enough to aid configurational assignments.

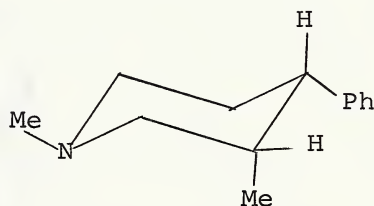
1,3-DIMETHYL-4-PHENYLPYPERIDINES:-

In an attempt to obtain α and β -1,3-dimethyl-4-phenyl-4-piperidinoamidines (79 and 80 respectively) by reacting the corresponding nitrile compounds with sodamide in boiling xylene (the object was to establish the stereochemistry of amidines unambiguously by chemical correlations) α and β -1,3-dimethyl-4-phenylpiperidines (127

and 126 respectively) were obtained. The α -isomer is considered to have the trans (3-Me/4-Ph) structure (127) and β -isomer the cis (3-Me/4-Ph) structure (126) (shown as the most probable conformations) on the following



127



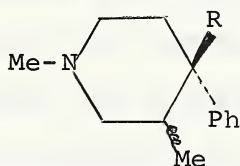
126

grounds:-

1. the 3-methyl signal of the β -isomer hydrochloride is at lower field than the 3-methyl signal of the corresponding α isomer (α -3-Me 44 Hz; β -3-Me 67 Hz from TMS in CDCl_3).
2. α -3-methyl signal displays virtual coupling effects (outer peak separation = 5 Hz) while the corresponding β -signal is a near-symmetrical doublet ($J = 7.5$ Hz) (cf. previous discussion of virtual coupling p.88) .

Examination of the PMR spectrum of the hydrocarbon (127) salt derived from the α -cyanide (78) reveals the presence of a low intensity doublet at 66 Hz in addition to the main sec-Me signal at 44 Hz. The former signal probably arises from the sec Me group of the β -isomer (126) . The hydrocarbon salt derived from the β -cyanide similarly displays major (66 Hz) and minor (44 Hz) sec Me signals. These results show that the removal of the ni-

TABLE VIII. 3-METHYL CHEMICAL SHIFT COMPARISONS OF
SOME 1,3-DIMETHYL-4-PHENYL-4-SUBSTITUTED PIPERIDINES
IN CDCl₃



No.	R	3-Me Chemical Shift ^a	
		α -isomer	β -isomer
1.	H	40	48
2.	OH	37.5 ^c	44 ^e
3.	OCOEt	41 ^c	44 ^e
4.	CN	48 ^c	45.5 ^c
5.	CO ₂ Et	64 ^c	45 ^c
6.	COEt	67 ^c	42 ¹

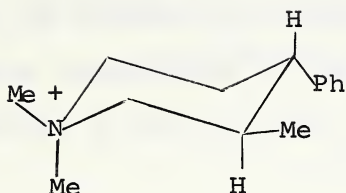
N.B. Notations used here have the same meaning as described in the footnotes of Table V and VI.

trile with sodamide (CN-H) takes place with small amount of inversion at C-4.

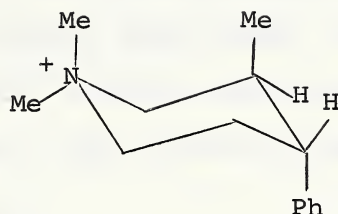
Knowledge of 3-methyl chemical shifts in the α and β -isomeric (127 and 126) also gives some idea of magnetic influence of other groups such as hydroxyl, cyano, carbethoxy, propionyl, etc. at C-4. An examination of Table VIII indicates that whereas the hydroxyl substituent has a shielding; the 4-cyano, 4-carbethoxy, 4-propionyl groups have a deshielding influence on the α -3-methyl signal in CDCl_3 .

The methiodide of β -1,3-dimethyl-4-phenylpiperidine exhibited a 3-Me doublet at 53 Hz in its PMR spectrum with CDCl_3 as solvent. However, when PMR spectrum of the corresponding α -isomer was determined, it exhibited two 3-methyl doublets at 48 Hz and at 54 Hz respectively. The presence of two doublets became clearer when the spectrum was determined in D_2O . This again points to the fact that the removal of the nitrile function by sodamide involves a small amount of inversion.

In the methiodide of α -1,3-dimethyl-4-phenylpiperidine, the more favoured conformation is clearly the chair form (140). Hence, two observed chemical shifts of N^{Me} (221 and 214 Hz) may be taken to represent axial and equatorial environments for the methyl groups. However, when CDCl_3 was replaced by D_2O as a solvent, a single N-methyl signal was obtained, a result which indicates that con-



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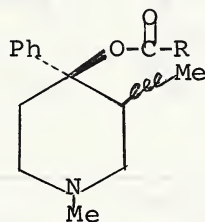
formers additional to the e-phenyl chair (140) must have significant populations in the polar solvent. The influence of solvent upon conformational equilibrium in piperidine salts is discussed more fully in the next section.

CONFORMATIONAL PREFERENCE OF DIASTEREOISOMERIC 3-METHYL-4-PHENYLPYPERIDINES IN WATER:-

The use of physical techniques such as IR and UV spectrophotometry, X-ray crystallography, etc. has yielded information concerning the conformation of molecules in the crystalline state and in solution in organic solvents. Much less information, however, is available concerning molecular conformation under aqueous biological conditions. Hydration may increase the effective size of an organic molecule in aqueous solution and thus have a vital influence upon its fit at a receptor.

A comparative study of the PMR characteristics of diastereoisomeric prodinols and their derived esters, as hydrochloride salts in D₂O (a solvent equivalent to water)

and CDCl_3 has provided evidence that conformational changes may be induced by a change of solvent (Casy 1968). Resonance signals due to the aromatic, N-methyl and acyloxy protons of the α - and β - ester (142) hydrochlorides in



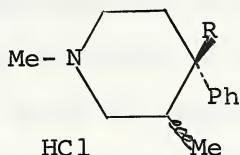
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where $\text{R} = \text{Me}, \text{Et},$
 $\text{n-C}_3\text{H}_7, \text{etc.}$

D_2O differed at most by only a few Hz from those of corresponding signals of the CDCl_3 spectra (TMS reference, internal in CDCl_3 , external in D_2O) and no pronounced difference between Δ values (chemical shift in D_2O minus chemical shift in CDCl_3) of α/β pair of signals was found. However, Δ values for the α - and β -3-methyl signals differed markedly (α - near zero; β near -20 Hz) the chemical shift difference values of these groups in D_2O being in sharp contrast to the difference displayed when CDCl_3 was the solvent (Table IX, No. 1-6). A similar, but smaller, solvent induced decrease in the chemical shift difference between α - and β -3-methyl groups was noted for the prodinol alcohols from which the esters were derived (Table IX, No. 7-8).

Similar spectral data were obtained for the present series of diastereoisomers (Table IX, No. 9-16). In all

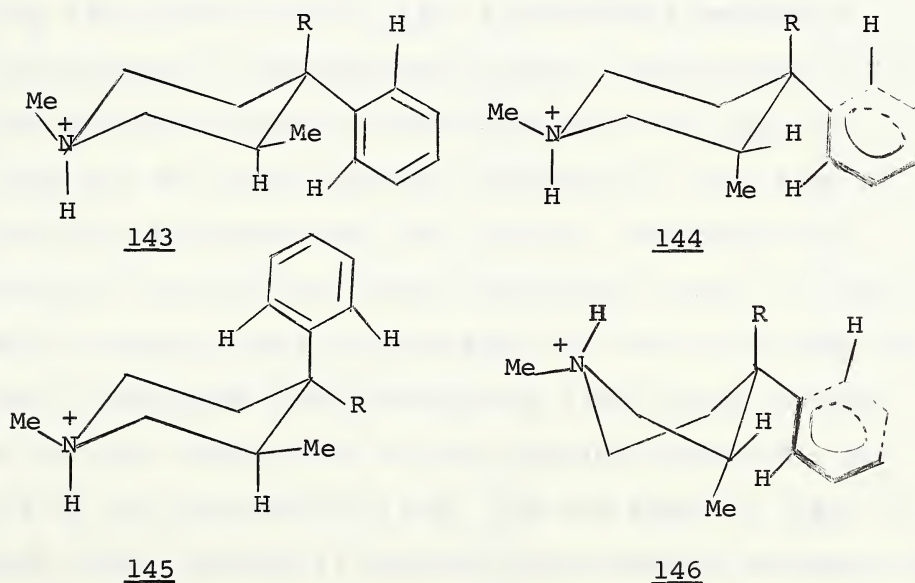
TABLE IX. 3-METHYL CHEMICAL SHIFT COMPARISONS IN D_2O
AND $CDCl_3$ OF α/β PAIR OF SIGNALS IN SOME 4-
4-PHENYLPYPERIDINE DERIVATIVES



No.	R	Isomer	3-Methyl Chemical Shift ^a		Dif. \triangle
			D_2O	$CDCl_3$	
1.	OCOMe	α	44 ^e	44 ^e	0
2.	OCOMe	β	41 ^e	61 ^e	- 20
3.	OCOEt	α	43.5 ^e	44 ^e	- 0.5
4.	OCOEt	β	43.5 ^e	62 ^e	- 18.5
5.	OCOnPr	α	40 ^e	44 ^e	- 4
6.	OCOnPr	β	42.5 ^e	61 ^e	- 18.5
7.	OH	α	37.5 ^e	39.5 ^e	- 2
8.	OH	β	45 ^e	58 ^e	- 13
9.	H	α	38 ^e	44 ^e	- 6
10.	H	β	44 ^e	67 ^e	- 23
11.	CN	α	47 ^e	51 ^e	- 4
12.	CN	β	42 ^e	66 ^e	- 24
13.	CO ₂ Et	α	57 ^c	58 ^c	- 1
14.	CO ₂ Et	β	45 ^e	62 ¹	- 17
15.	COEt	α	67 ¹	67 ¹	0
16.	COEt	β	39 ^e	61 ^e	- 22

N.B. Notations used here have the same meaning as described in the footnotes of Table V and VI.

instances the 3-methyl chemical shift of the β -members of diastereoisomeric pairs moves upfield by about 20 Hz when CDCl_3 is replaced by D_2O as a solvent while the corresponding α -resonance position is little affected. Hence the deshielding influence of protonated nitrogen upon the β -3-methyl group is reduced when CDCl_3 is replaced by D_2O , a result which is considered due to a solvent induced decrease in the conformational preference of the axial 3-methyl conformers (144) i.e. those in which the $\text{NH}^+\text{-Me}$ distance is a minimum. Of alternative conformations, both the axial 4-phenyl chair (145) and the skew boat conformation (146) place the protonated nitrogen at



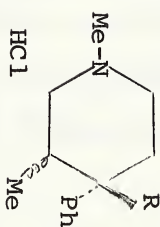
a greater distance from the 3-methyl group, the chemical

shift of this group then being expected to approach that of 3-methyl in the α -isomer (143). Evidence of the relative importance of conformations (145) and (146) may be derived from a consideration of the probable orientations of the aromatic and piperidine rings and the likely influence of the aromatic group upon the acyloxy proton signals of the reversed esters ($\text{O}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}_2-\text{Me}$), the ethoxy-carbonyl signals of the normal esters ($\text{CO}_2-\text{CH}_2-\text{Me}$) and the propionyl signals of the ketones (COCH_2Me) (Table X). In the skewboat (146) the steric disposition of the 4-phenyl and 3-methyl substituents is similar to that obtained in the equatorial 4-phenyl chair (144), in which a perpendicular orientation of the aromatic and piperidine ring planes (as in 143) is unfavoured because of ortho-aromatic hydrogen-axial methyl interactions. The more probable aromatic orientation shown in (144) (in which the two rings approach coplanarity), will have a shielding influence upon the acyloxy, carbethoxy and propionyl protons for reasons previously given. In the axial 4-phenyl chair conformation, of the two extreme aromatic piperidine ring orientations (aryl plane coplanar or at right angles with a plane passing through N-1 and C-4 of the heterocyclic ring), the one shown in (145) is more likely because it removes ortho-aromatic hydrogen from the vicinity of the equatorial 3-methyl group (Allinger, *et. al.* 1962). In conformation (145), the 4-oxygenated function does not pass above the aromatic plane during the

TABLE X. COMPARISON OF CH_2Me AND $\text{CH}_2\text{-Me}$ GROUP CHEMICAL SHIFT DIFFERENCE

IN D_2O AND CDCl_3 OF α / β PAIRS OF SIGNALS IN SOME 1,3-DI-

METHYL-4-PHENYL-4-PIPERIDINO ESTERS AND KETONES



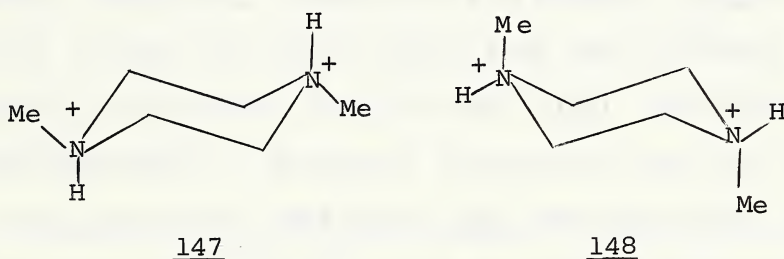
No.	R	Isomer	$\text{CH}_2\text{-Me}$ D_2O	$\text{CH}_2\text{-Me}$ CDCl_3	DIFFERENCE Δ	$\text{CH}_2\text{-Me}$ D_2O	$\text{CH}_2\text{-Me}$ CDCl_3	DIFFERENCE Δ
1.	CO_2Et	α	260 ^h	259 ^h	+1	74 ^l	76 ⁱ	-2
2.	CO_2Et	β	250 ^h	250 ^h	0	67 ⁱ	67 ^{i,k}	0
3.	COEt	α	130, 157 ^o	133 ^h	-3, +24 ^p	54, 38	59 ⁱ	-5, -21
4.	COEt	β	137 ^h	132 ^h	+5	44 ⁱ	53 ⁱ	-9
5.	OCOEt	α	155.5 ^h	155.5 ^h	0	69.5 ⁱ	73.5 ⁱ	-4
6.	OCOEt	β	146 ^h	143 ^h	+3	62 ⁱ	64 ⁱ	-2

N.B. Notations used here have the same meaning as described in the footnotes of Tables V and VI. Protonation of the α -ketone gives epimers which complicate the PMR signals.

course of its rotation about the C_4-O bond, the phenyl-acyloxy, carbethoxy, propionyl, etc. orientation being similar to that present in the preferred α conformer (143) (in α -isomers, conformational preferences are probably alike in both $CDCl_3$ and D_2O). Hence, the fact that the chemical shifts of the β -4-oxygenated groups are upfield of the corresponding α -signals and in extents that do not differ significantly from those observed in $CDCl_3$, (Table X) together with the large $-\Delta G_x$ value of a phenyl substituent in saturated, six-membered cyclic systems (3.1 K cal/mole is an average value, Eliel, et. al. 1965), support the skewboat (146) as the preferred conformation of the β -derivative hydrochlorides when dissolved in D_2O .

The changes in conformational equilibria induced by solvent changes may be accounted for in terms of solvation effects. A considerable increase in the degree of solvation of both the protonated basic centre and the oxygen function at C-4 is probable when $CDCl_3$ is replaced by D_2O as solvent; in consequence, the effective bulk of these structural features should become greater. While such increases should not significantly alter conformational preferences in the α -derivatives, preferences for the conformer (144) would be expected to decrease, since the destabilizing methyl ^+NH and oxygen function $-H$ 1,3-diaxial interactions obtained in (144) will be larger in the more solvated molecule. It is known, for example, that

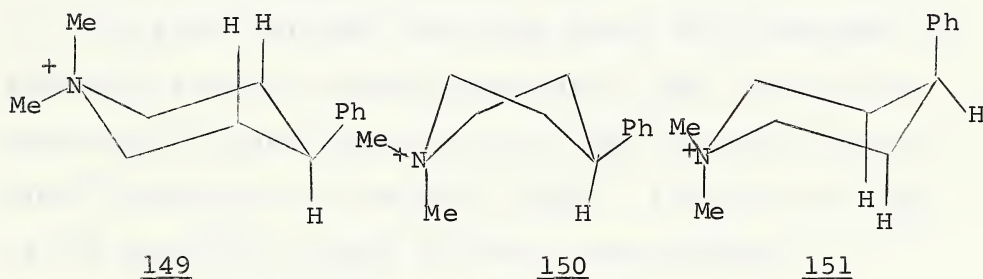
the $-\Delta G^\circ$ value of the hydroxyl group is significantly greater in D_2O than in CCl_4 (1.0 for CCl_4 , 1.25 for D_2O at 28°) (Anet 1962). Sudmeier and Occupati (1968) from NMR studies of N,N-dimethylpiperazine in aqueous hydrochloric acid found that the energy difference between the two chair conformers (147) and (148) (1.16 ± 0.1 k cal/mole at 25°) was significantly smaller than that an-



anticipated on the basis of the relative sizes of a methyl group and a bare proton. The small value of $-\Delta G^\circ$ supports the view that the effective size of NH protons is increased by a sphere of tightly bound water molecules. Solvation effects would also be expected to raise the energy of the skewboat (146) (through enhanced bow sprit flagpole substituent interactions), but the influence of solvent is considered to be more significant in the β -chair where four non-bonded interactions are involved.

The postulate of a skewboat conformation being favoured in a piperidine derivative when 1,3-diaxial interactions in the corresponding chair are enhanced through solvation effects is supported by the solvent dependence

of N-methyl chemical shifts in some piperidine methiodides. The methiodide of 1-methyl-4-phenylpiperidine displays well separated N-methyl PMR signals at 217 and 205 Hz from TMS (60 MHz) in CDCl_3 . N-Methyl signal separation is much reduced, however, in D_2O (3 Hz separation) and DMSO (zero separation) (Casy and Parulkar, unpublished results). This result demonstrates the smaller environmental difference between the two N-methyl groups in the polar solvents as would result from the existence of comparable populations of e-Ph chair (149) and skewboat (150) conformations. 1,3-Diaxial interactions are not relieved in the a-Ph chair conformer (151) and this fact, together with the large $-\Delta G^\circ$ value of phenyl substituents in



saturated, six-membered cyclic systems, suggest that its populations will be low.

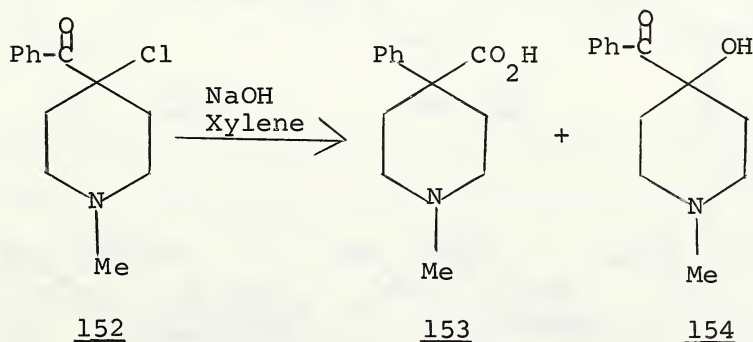
INVESTIGATION OF ALTERNATIVE ROUTES TO ISOMERIC

3-METHYL-4-PHENYL-4-PIPERIDINONITRILES

Initial difficulties encountered in the cyclization routes to isomeric 4-phenyl-4-cyanopiperidines prompted the investigation of alternative synthetic pathways. Although none of these routes led to the synthesis of the desired products (see section on aims and objects), certain novel results of interest occurred during the course of the work and these aspects are described at appropriate points.

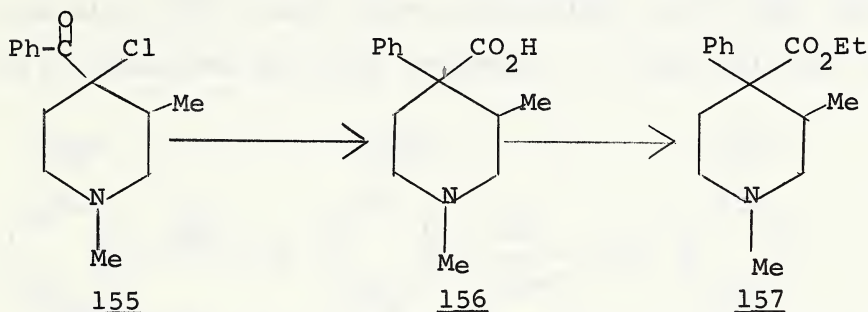
1. ROUTE BASED ON THE QUASI-FAVORSKII REARRANGEMENT OF 4-BENZOYL-4-CHLORO-1-METHYLPYPERIDINE:-

In 1959, Smismann and Hite found that treatment of 4-benzoyl-4-chloro-1-methylpiperidine (152) with sodium hydroxide in xylene gave the acid (153) related to pethidine, in addition to the ketol (154). Formation of (153) is the result of a quasi Favorskii rearrangement

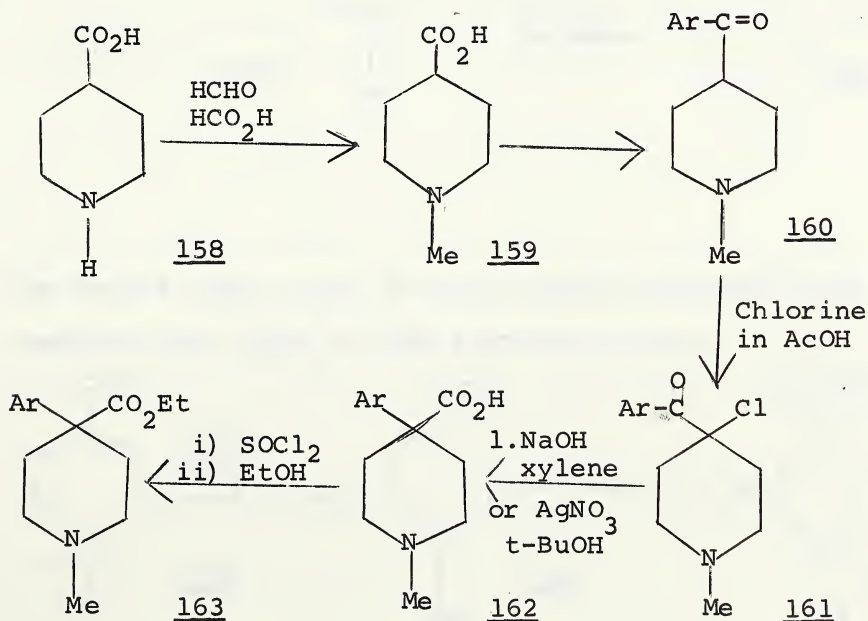


of the 4-benzoyl derivative (152). (This rearrangement differs from the normal Favorskii rearrangement in, that

the non-halogenated α -carbon bears no hydrogen atom). The same reaction using the 3-methyl analogue (155) as substrate is a potential route to the 3-methyl-pethidines (157). As a first series of experiments, the original

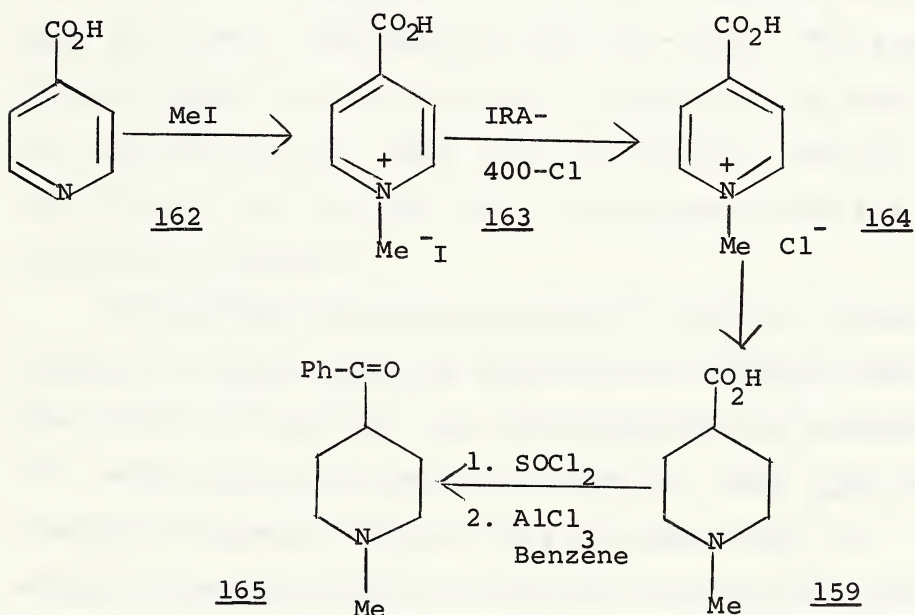


sequence of Smissman and Hite (1959) was repeated to gain experience of reaction conditions and to see if the yield of the rearranged product (i.e. the acid 156) could be improved. The following sequence of reactions was planned:

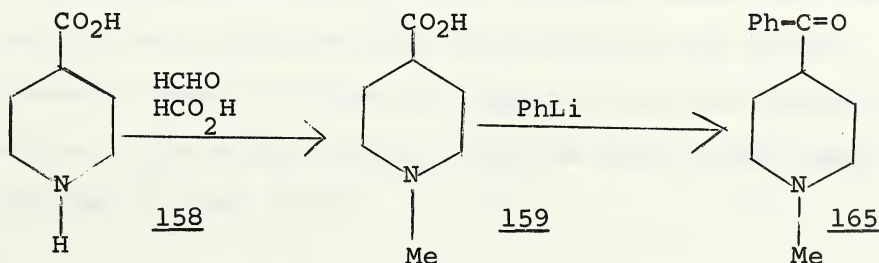


where Ar may be phenyl, *p*-tolyl, 2-thienyl, 2-furyl, etc.

A convenient method of obtaining N-methyl-4-piperinophenyl ketone (165) was first sought. Literature methods (Villani 1952, Sugimoto and Kugita 1953; Smismann and Hite 1959) start from isonicotinic acid (162) and are cumbersome and time consuming. It was believed that



the ketone (165) might be more readily obtained from isonipecotic acid (158) by the following route:

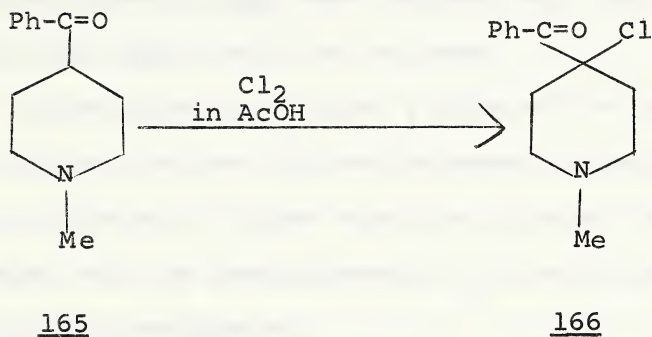


Isonipecotic acid (158) which was commercially available was reacted with $\text{HCHO} + \text{HCO}_2\text{H}$ to give the corresponding N-methyl compound (159), isolated as its hydrochloride. The corresponding formate salt was isolated directly from the reaction product. The acid (159) hydrochloride was converted into its free base by an anion exchange technique using Rexyn RG-1 as exchange resin, and the base (159) purified by sublimation (m.p. $172-173^\circ$). The same compound (159) was also obtained in good yield by treating isonipecotic acid (158) with 37% formalin, palladized-charcoal and hydrogen gas at room temperature and atmospheric pressure.

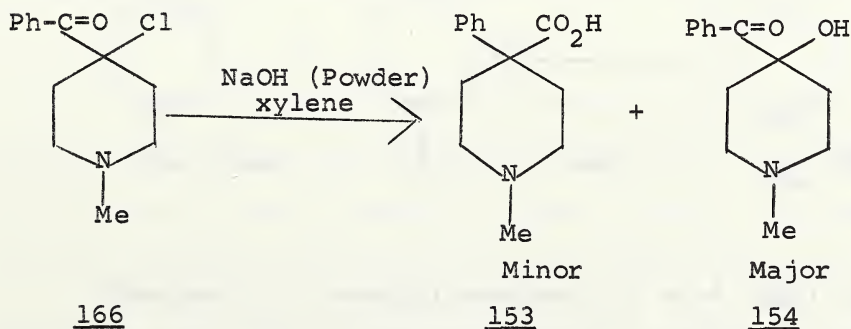
The product contained one mole of water of crystallization as shown by its IR spectrum and elemental analyses; after sublimation, the anhydrous base was obtained.

When anhydrous N-methylisonipecotic acid (159) was treated with phenyl lithium (Casy and Myers 1965), N-methyl-4-piperidinophenyl ketone was obtained which gave a hydrochloride melting at $204.5-205.5^\circ$. Smismann and Hite (1959) reported the melting point $209-210^\circ$ for the same compound prepared from isonicotinic acid (162). In view of the difficulties experienced in procuring N-methylisonipecotic acid in the anhydrous base form, the reaction was attempted with the hydrochloride itself. Excess of phenyl lithium was used to allow for neutralization of the acidic proton, and the same ketone (165) was obtained in good yield.

N-Methyl-4-chloro-4-piperidinophenyl ketone (166) hydrochloride was obtained by chlorination of N-methyl-4-piperidinophenyl ketone (165) hydrochloride following Smissman and Hite's (1959) procedure.



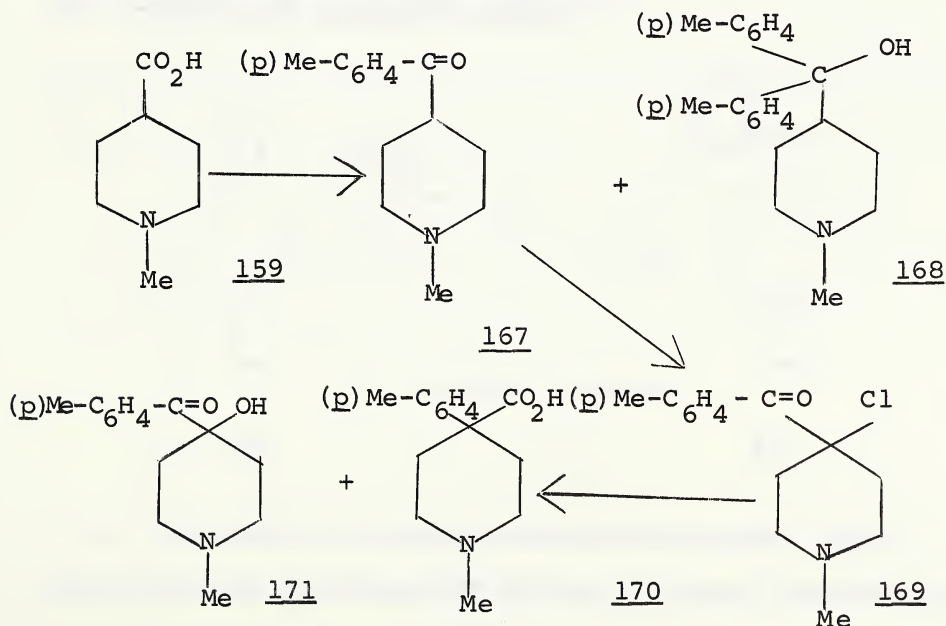
When N-methyl-4-chloro-4-piperidinophenyl ketone (166) was treated with powdered and dried sodium hydroxide and boiling xylene (i.e. the quasi-Favorskii Rearrangement conditions used by Smissman and Hite 1959), N-methyl-4-phenyl-4-piperidinocarboxylic acid (153) and N-methyl-4-hydroxy-4-piperidinophenyl ketone (154) were obtained as minor and major products, respectively.



In an attempt to obtain higher yields of the acid (153), the rearrangement was carried out by AgNO_3 - t -BuOH as this reagent had been reported to be a better catalyst for this reaction (Lyle *et. al.* 1961). In this case, the undesired alcohol (154) was obtained as a main product and no acid (153) could be isolated.

In the hope that higher yields of the carboxylic acids may be obtained by rearrangement of ketones containing aryl groups of higher electron release character, the syntheses and the rearrangements of the following compounds were investigated:

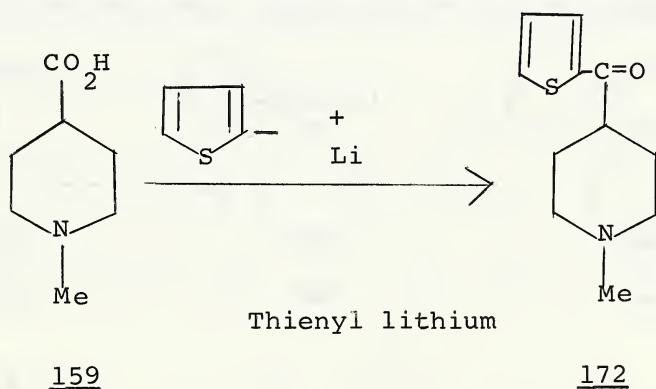
I) P-TOLYL GROUP:-



Treatment of N-methylisopiperidic acid (159) hydrochloride with excess of p-tolyllithium resulted in the

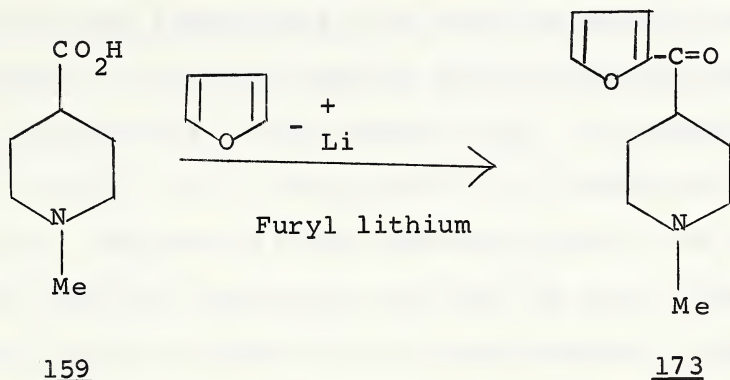
formation of N-methyl-4-piperidino-p-tolyl ketone (167) and N-methyl-4-piperidinoditolyl carbinol (168). When the ketone (167) hydrochloride was treated with chlorine in glacial acetic acid in the usual way, N-methyl-4-chloro-4-piperidino-p-tolyl ketone (169) hydrochloride was obtained in good yield and was shown to contain one mole of water (IR and elemental analyses evidence). When the α -chloroketone (169) was treated with powdered sodium hydroxide and boiling xylene as usual, N-methyl-4-hydroxy-4-piperidino-p-tolyl ketone (171) was obtained as the major product and N-methyl-4-phenyl-4-piperidino-carboxylic acid (170) only in traces.

II) 2-FURYL AND 2-THIENYL GROUPS:-

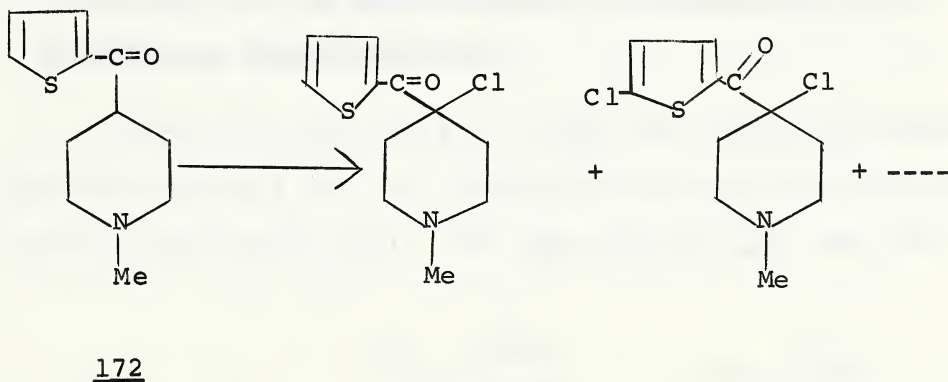


Treatment of N-methylisonipecotic acid (159) hydrochloride with excess of 2-thienyl lithium (obtained by exchange of Li from phenyl to thienyl group) provided N-methyl-4-piperidinothienyl ketone (172) which was isolated as its hydrochloride monohydrate. Similarly, when N-methylisonipecotic acid (159) hydrochloride was treated

with excess of 2-furyl lithium, the corresponding furyl ketone (173) was obtained, also isolated as a hydrochloride.



When N-methyl-4-piperidino-2-thienyl ketone (172) hydrochloride was treated with chlorine gas in glacial acetic acid, a mixture of products was obtained which could not be resolved. Substitution of the thienyl ring,

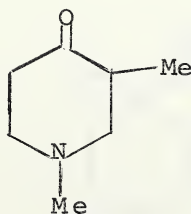


in addition to chlorination at C-4 was deduced from the appearance of more than one carbonyl band in the IR spectrum of the product, a result considered due to excess passage of chlorine. As the exact amount required of chlorine, could not be conveniently controlled, attention

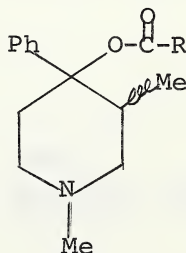
was directed to α -bromination of the ketone (172) by bromine in chloroform (Lyle 1961). When 1-methyl-4-piperidino-2-thienyl ketone (172) was subjected to bromination at room temperature, the starting material was recovered. In view of similar difficulties envisaged with the corresponding 2-furyl ketone (173), no attempt was made to carry out α -chlorination or bromination on that compound. Moreover as the undesired alcohol was the major and the desired carboxylic acid was the minor constituent of the reaction mixture in all rearrangements studied, the formation of pethidine derivatives via this route and the corresponding 3-methyl analogues by a modification of the above scheme were not pursued further.

2. ROUTE BASED ON THE REARRANGEMENT (OR DEGRADATION) OF A 4-BENZOYL-4-PHENYLPIPERIDINE:-

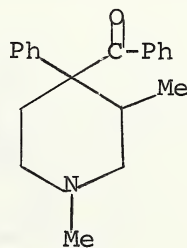
3-Methyl-4-piperidones e.g. (174) are readily available starting materials for the synthesis of 4-phenyl-4-acyloxy-3-methylpiperidines (175). The same ketone (174) may also



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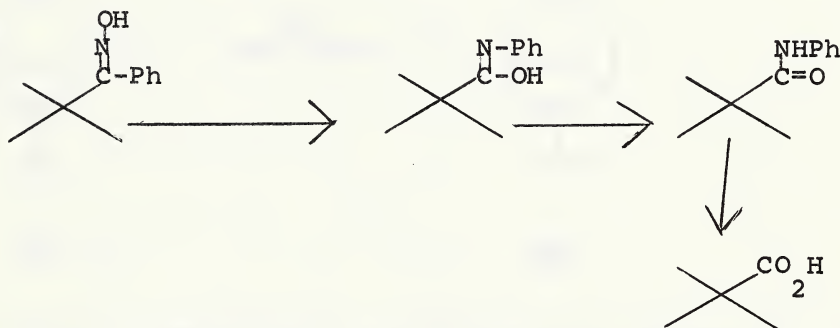


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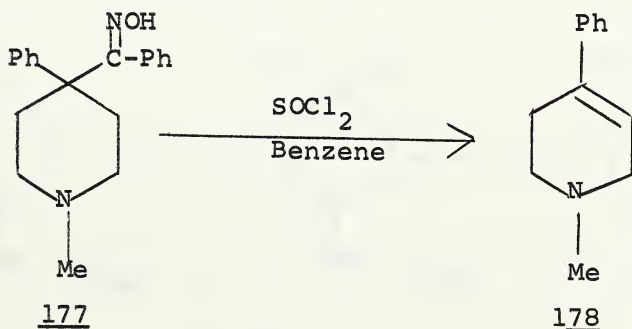


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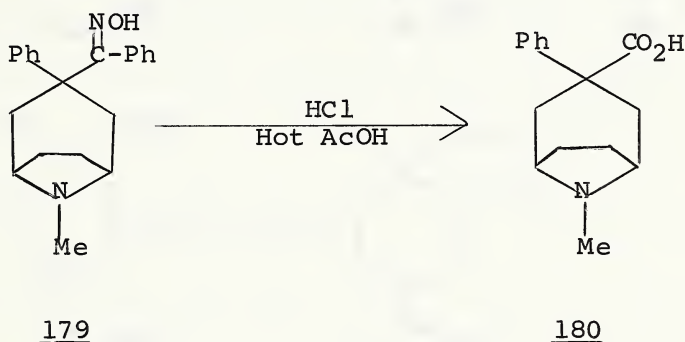
be converted to 4-benzoyl analogues (176) and hence may serve as a precursor of pethidine derivatives provided a means may be found for converting the 4-benzoyl function to a 4-carboxylate group. One possible way of achieving this would be by the Beckmann rearrangement of the corresponding oxime, when phenyl is the migrating group.



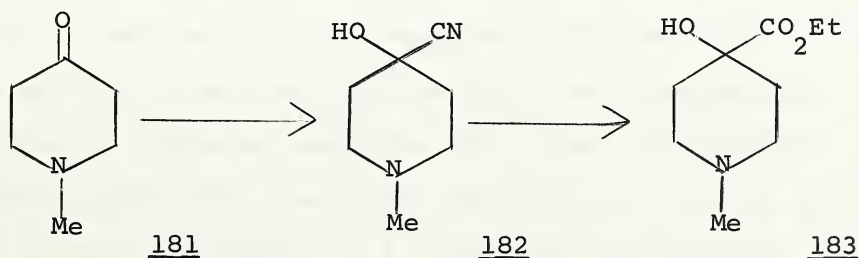
This reaction has, in fact, been studied by Lyle and Lyle (1953) for the oxime of 4-benzoyl-1-methyl-4-phenylpiperidine. When the oxime (177) was reacted with thionyl chloride in dry benzene, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (178) was obtained. In an attempt to rearrange the oxime (177) by hydrogen chloride in acetic

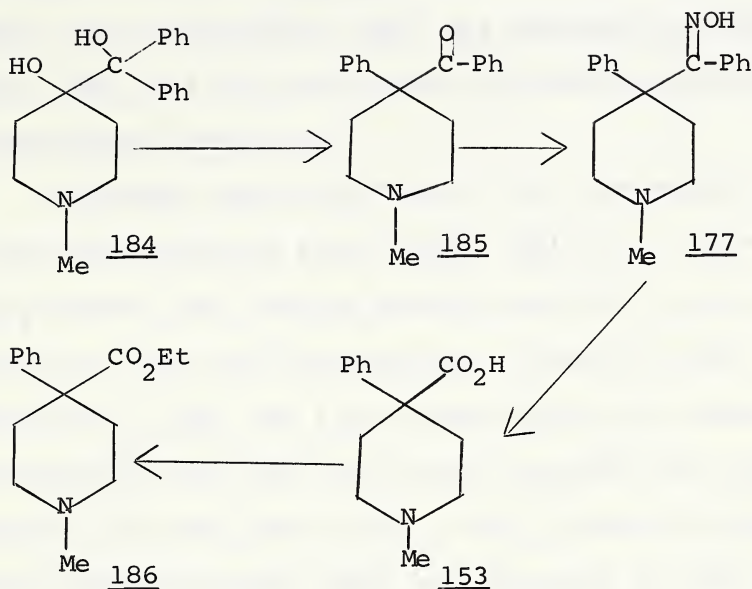


acid (vigorous conditions used), these workers obtained only a trace of cleavage product (178) and the remainder of the material was recovered. The majority of this report seemed surprising since the corresponding tropane



oxime (179) is reported to yield the carboxylic acid (180) in good yield when rearranged by hydrogen chloride in hot acetic acid (Bell and Archer 1960). In view of these conflicting results, it was decided to reinvestigate the Beckmann rearrangement of the oxime (177) by strictly adhering to the Bell and Archer procedure (1960). The following sequence of reactions was planned:-





N-Methyl-4-cyano-4-piperidinol (182) was prepared by reacting N-methyl-4-piperidone (181) with a mixture of KCN and HCl in water (Lyle and Lyle 1954). When the reaction product was extracted with ether (as reported) a very low yield of the cyanohydrin (182) was obtained. However, continuous extraction with ether using a liquid-liquid extractor provided the cyanohydrin (182) in 83% yield. There are various reports of the feasibility of the production of cyanohydrins from the corresponding ketones by exchange reactions with other cyanohydrins. Acetone cyanohydrin has been used recently for the synthesis of the cyanohydrin of 1,3-dimethyl-4-piperidone and a high yield was reported (Nazarov et. al. 1955). When

N-methyl-4-piperidone (181) was treated with acetone cyanohydrin, the cyanohydrin (182) was obtained in excellent yield (96%) and this convenient procedure was utilized in subsequent reactions.

Attempted esterification of the cyanohydrin (182) to the corresponding ethyl ester (183) by a one-step H_2SO_4 -ethanol and benzene method resulted in recovery of most of the starting material. However, when the cyanohydrin (182) was first hydrolyzed with concentrated hydrochloric acid and the product treated with H_2SO_4 -ethanol (Lyle and Lyle 1954), ethyl N-methyl-4-hydroxy-4-piperidinocarboxylate (183) was obtained in good yield.

The reaction of phenyl lithium with the above ester (183) provided 1-methyl-4-hydroxy-4-piperidinodiphenyl carbinol (184) which melted within the reported range. The corresponding hydrochloride had a lower melting point than the literature value and proved to be a monohydrate.

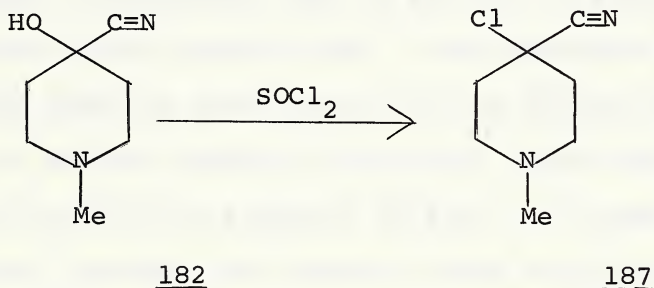
The rearrangement of N-methyl-4-hydroxy-4-piperidinodiphenyl carbinol (184) hydrochloride with ZnCl_2 and acetic anhydride (Lyle and Lyle 1954) afforded N-methyl-4-phenyl-4-piperidinophenyl ketone (185).

When the ketone (185) was reacted with hydroxylamine hydrochloride and pyridine by heating, following the general procedure outlined by Bachmann and Barton (1938), the oxime (177) was obtained directly as its hydrochloride which on recrystallization from ethanol melted at 267° . The identity of this product was confirmed by elemental

analyses, IR data (presence of C=N and OH bands and absence of carbonyl band) and a positive silver nitrate test. Lyle and Lyle (1954), however, obtained the free base (m.p. 186-188°) using the same procedure.

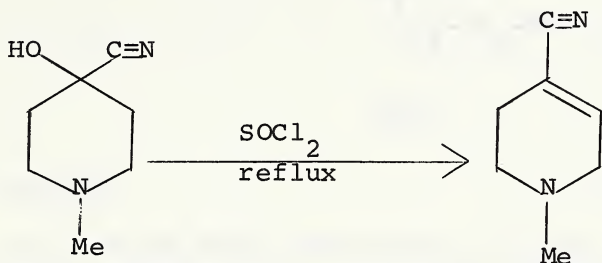
When the above oxime (177) hydrochloride was subjected to the action of hydrogen chloride in hot acetic acid i.e. the rearrangement conditions successfully applied to the tropane analogue (179) by Bell and Archer (1960), the starting material was recovered.

In the course of these investigations, it was considered of interest to prepare N-methyl-4-chloro-4-cyanopiperidine (187) from the corresponding cyanohydrin and thionyl chloride because the chlorocyanide (187) was of potential value as an intermediate (e.g. for the prep-



aration of 4-benzoyl-4-chloro-1-methylpiperidine, 4-benzoyl-4-phenyl-1-methylpiperidine, 4-cyano-4-phenyl-1-methylpiperidine, etc.). When N-methyl-4-hydroxy-4-cyanopiperidine was treated with thionyl chloride in chloroform, the hydrochloride of the starting material was obtained. When N-methyl-4-hydroxy-4-cyanopiperidine (182) hydrochloride was heated under reflux with thionyl

chloride in the absence of solvent, a new compound was formed, melting at 175-176°. This compound was assigned the structure N-methyl-4-cyano-1,2,5,6-tetrahydropyridine (188) hydrochloride on the basis of IR and PMR spectro-

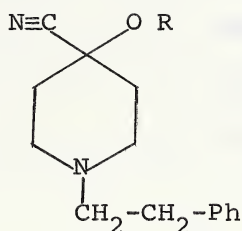


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scopic data and elemental analyses.

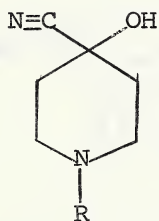
Beckett and coworkers (1954, 1956) considered that the presence of a suitably oriented flat aromatic ring played an important role in the fit of an analgesic at a postulated receptor site. The importance of a phenyl group might be associated with its delocalized π electrons and the possible role which these might play in bonding with the receptor surface. In order to investigate, whether the aromatic group could be replaced by other groupings, which, although non-aromatic possess a π cloud of electrons, Harper and Fullerton (1961) prepared compounds of the type (189) and tested them for analgesic action. These workers noted that conversion of N-phenethyl-4-cyano-4-hydroxypiperidine to its acetoxyster gave a compound with pronounced central nervous system activity whereas the corresponding propionoxyster



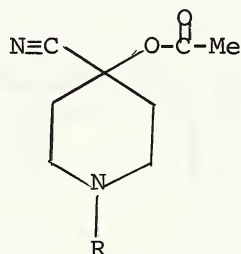
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was inactive.

In view of this observation, it was considered worthwhile converting N-methyl-4-cyano-4-hydroxypiperidine (182) to the corresponding acetate and testing the analgesic activity of this ester. When N-methyl-4-cyano-4-hydroxypiperidine (190R=Me) was treated with acetic anhydride-pyridine by heating to reflux, the desired ester (191R=Me) was obtained as its hydrochloride salt.

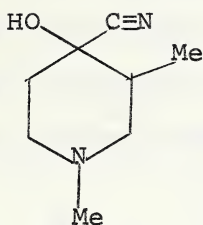


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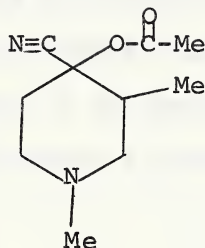


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The N-phenethyl analogue of (191, $R=(CH_2)_2Ph$) was also prepared from the N-phenethyl-4-piperidone (190; $R=(CH_2)_2Ph$), so that comparative data upon N-methyl and N-phenethyl acetates could be obtained. 1,3-Dimethyl-4-cyano-4-acetoxypiperidine (193) was also synthesized from the corresponding cyanohydrin (192) because the introduction



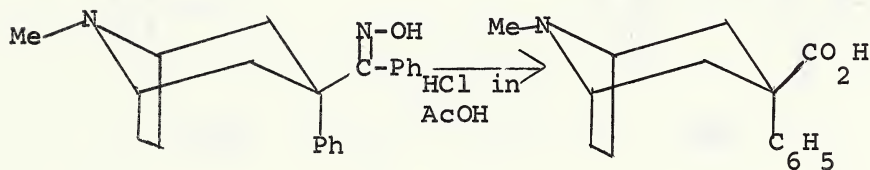
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of 3-methyl substituent has proved advantageous in reversed esters of pethidine.

As previously mentioned, Bell and Archer (1960) subjected α -3-phenyl- β -3-benzoyltropane oxime (194) to the Beckmann rearrangement by the action of hydrogen chloride in hot acetic acid and obtained 3- α -phenyl-3- β -

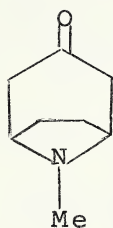


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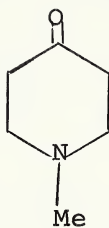
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tropanecarboxylic acid (195) in good yield. That the oxime was affected at all under these conditions is surprising since the piperidine analogue is unchanged by the same or a similar (Lyle and Lyle 1953) treatment. The reason for the differing reactivities of oximes of the

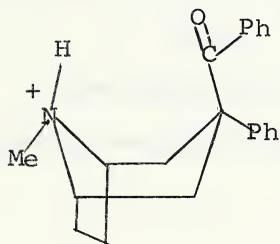
tropane and piperidine ketones (194 and 177 respectively) may be due to the likelihood of the two oximes differing in their favoured conformations. There is IR spectroscopic evidence that the ketone (196) adopts a preferred



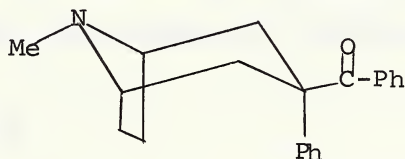
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boat or skewboat conformation (197) (Bell and Archer 1960); therefore, it is likely that the corresponding oxime also

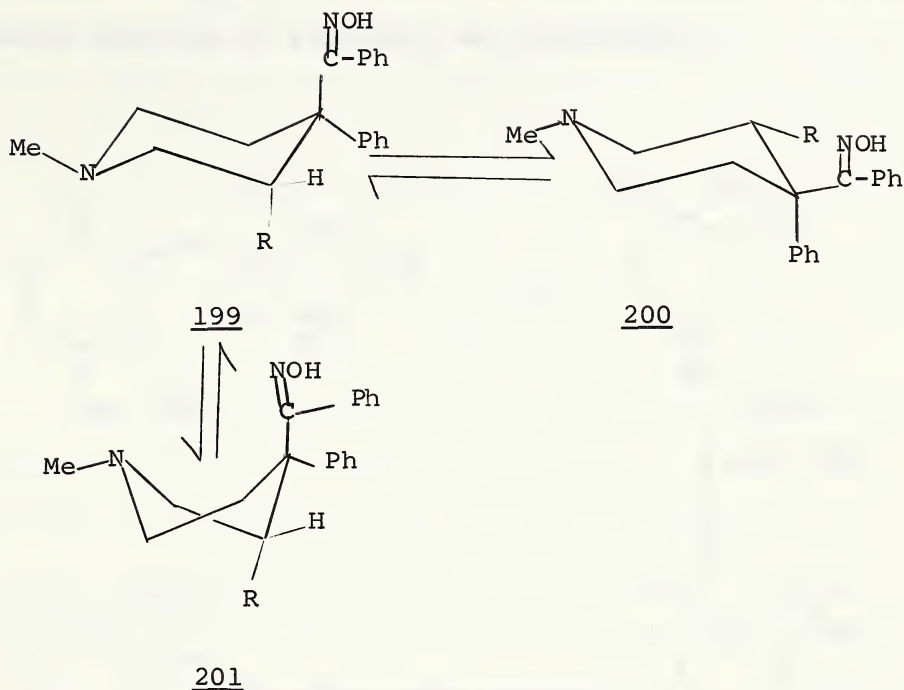


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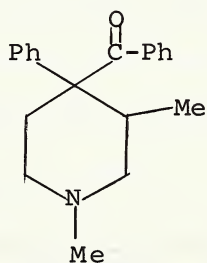


198

tends to adopt this arrangement or the a-Ph chair (194). In the piperidine analogue, however, the preferred conformation is likely to be the e-Ph chair (199) on the basis of phenyl group having the larger steric requirements. The skewboat (201) and/or the a-Ph chair (200) will be favoured more when a 3-Me group cis to 4-Ph is present because 1,3-diaxial interactions of the 3-a-Me group are reduced in these conformers.

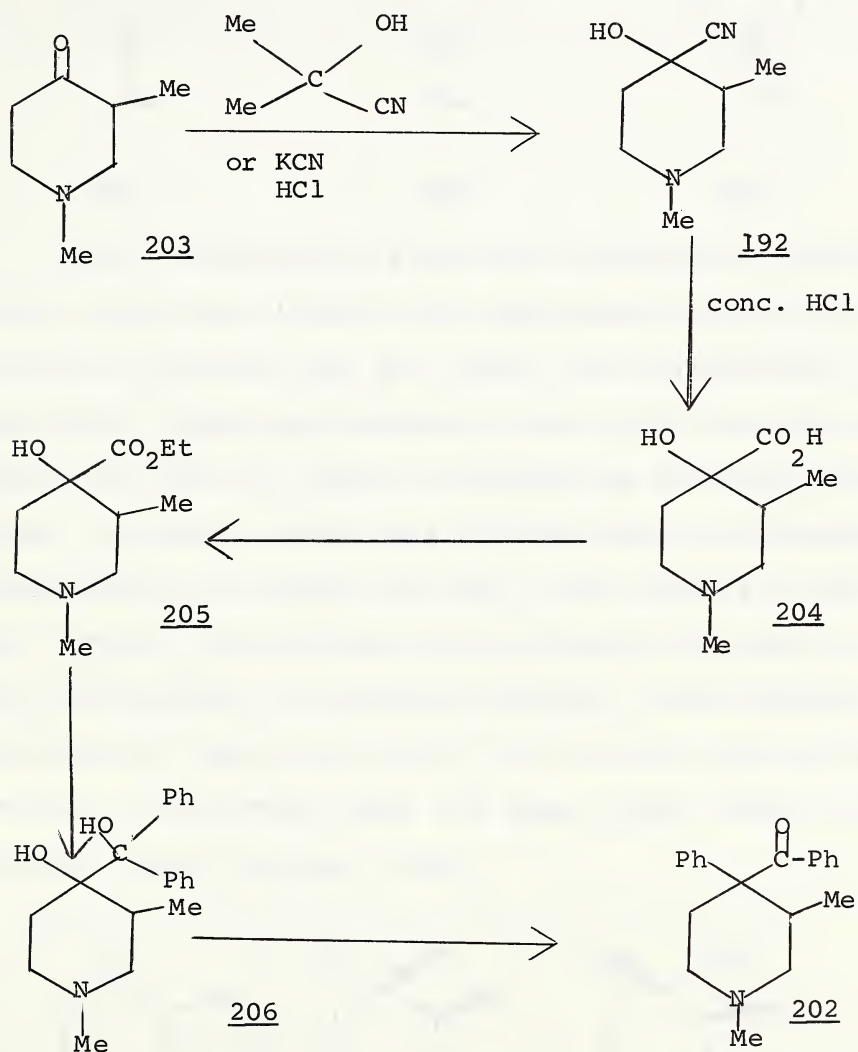


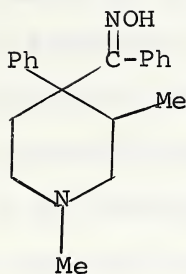
The synthesis of the 3-Me analogues (202) from 1,3-dimethyl-4-piperidone (203) has been reported (Unkovskii et. al. 1961) but the stereochemistry of the reaction sequence used has not been studied. It was, therefore, considered worthwhile investigating the stereochemistry of these reactions with a view to obtain the cis (3-Me/4-Ph) isomer and sub-



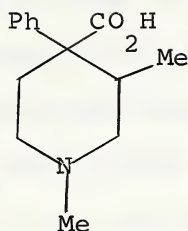
203

jecting its oxime to the Beckmann rearrangement. The following sequence of reactions was undertaken:

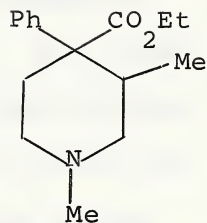




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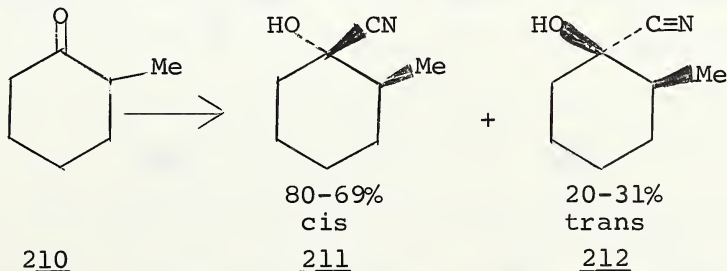


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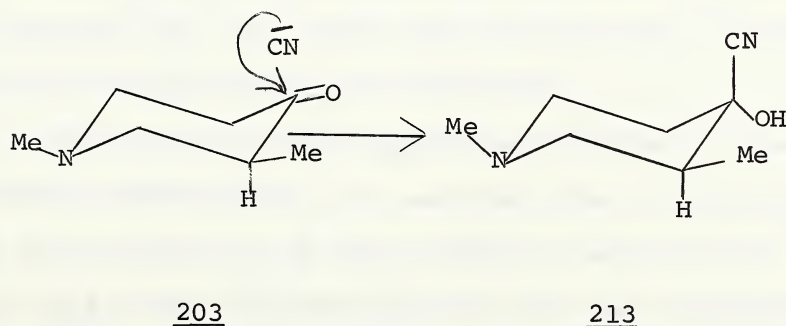
209

When 1,3-dimethyl-4-piperidone (prepared by Howton's (1945) method) was treated with acetonecyanohydrin according to Unkovskii *et. al.* (1961) the corresponding cyanohydrin (192) was obtained in high yield but only one isomer (m.p. 89-91°) could be isolated as previously reported. A similar result was obtained when 1,3-dimethyl-4-piperidone was treated with KCN. This failure to detect isomeric cyanohydrins is in contrast with results with the non-basic cyclohexane analogue. When 2-methylcyclohexanone (210) was treated with acetone cyanohydrin, a mixture of *cis* Me/CN (211) and *trans* (212) isomers was obtained (Nazarov *et. al.* 1955).



In a rigid or biased system, a reaction at the car-

bonyl carbon by a reagent such as Li AlH_4 or KCN-HCl may involve equatorial attack to give an axial alcohol or axial attack to give an equatorial alcohol. The former mode of reaction involves attack from the less hindered side of the function and may be said to be a result of steric approach control of the reaction. The latter mode often produces the more stable product and is said to be governed by product development control. Kamernitzky (1962) studied the spatial direction of addition reactions to non-basic cyclic ketones and observed, that the CN^- nucleophile attacked preferentially from the axial side to yield the a-CN/e-OH cyanohydrin (product development control). On the basis of these results, and the configuration of the major isomer obtained from 2-methyl-cyclohexanone, the cyanohydrin (192) probably has a cis (3-Me/4-CN) configuration (213) (it will be shown, subsequently, that this assignment is correct).



When 1,3-dimethyl-4-hydroxy-4-cyanopiperidine (192) was hydrolyzed with concentrated hydrochloric acid (Un-

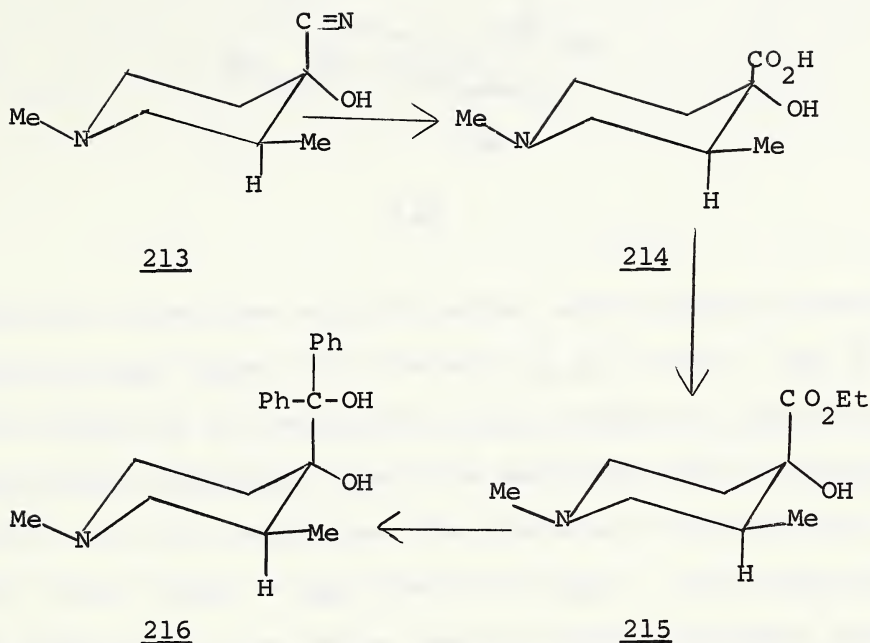
kovski, et. al. 1961), it was converted to the corresponding hydroxy acid (204) which was separated as a hydrochloride salt.

The hydroxy acid (204) hydrochloride was esterified with H_2SO_4 -ethanol to provide the corresponding ethyl ester (205).

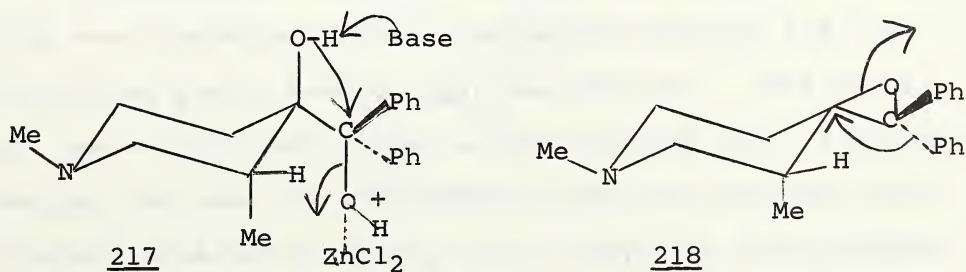
Reaction of ethyl 1,3-dimethyl-4-hydroxy-4-piperidinocarboxylate (205) with phenyl lithium yielded 1,3-dimethyl-4-hydroxy-4-piperidinodiphenylcarbinol (206), isolated as a hydrochloride (m.p. 262-263°). Unkovskii, et. al. (1961) prepared the same compound from the corresponding methyl ester.

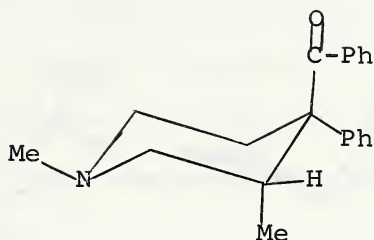
When the diol (206) hydrochloride was rearranged under the influence of anhydrous $ZnCl_2$ -acetic anhydride (Unkovskii et. al. 1961), the desired 1,3-dimethyl-4-phenyl-4-piperidinophenyl ketone (202) was obtained. The identity of this material was established by comparison of the melting point of this product with that reported by Unkovskii et. al. (1961) and from IR data. It formed a hydrochloride melting at 275-275.5°.

Before this ketone (202) was subjected to the Beckmann rearrangement, it was desirable to establish the stereochemistry of this compound unequivocally. Assuming a cis 3-Me/4-CN configuration for the cyanohydrin (213), the configuration of the diol (216) must be cis 3-Me/4-CPh₂OH since the reactions (213)→(216) are unlikely to involve a configurational change. However, the



preferred conformation of the diol (206) will be the piperidine chair-e-CPh₂OH conformation (217) rather than (216) on account of the large bulk of the CPh₂OH group. 1,3-Dimethyl-4-phenyl-4-piperidinophenyl ketone (202) may then arise from the corresponding carbinol (217) by the following mechanism:-

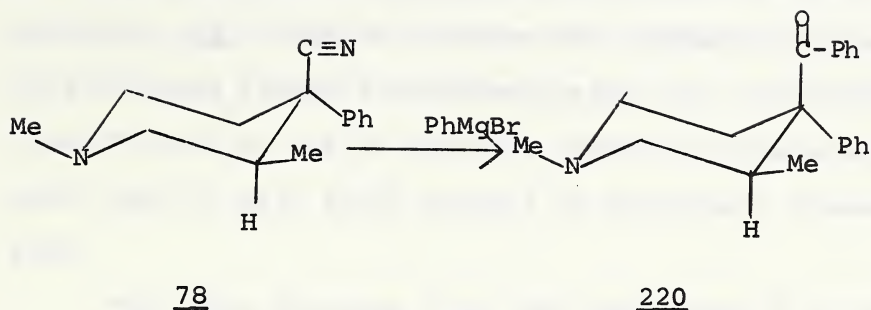




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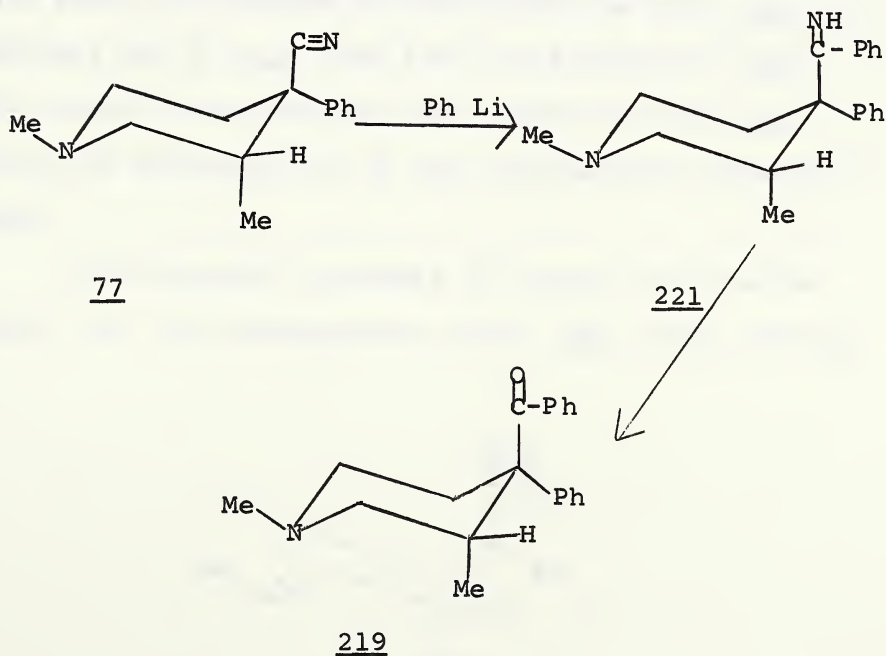
(epoxide formations exhibit second order reaction kinetics; Winstein and Lucas 1939; Warner, et. al. 1948). The β - configuration of the epoxide (i.e. projecting upwards is a reasonable assumption from this mechanism (Bell and Archer 1960). By this mechanism, the predicted configuration of the ketone (202) is cis 3-Me/4-Ph (219). This deduction is supported by the large chemical shift difference between the 3-methyl signal of the base and the hydrochloride of the ketone (202). Finally this assignment was unambiguously confirmed by converting both α and β -1,3-dimethyl-4-phenyl-4-piperidinonitrile, isomers of established configurations (discussed earlier), into the corresponding phenyl ketones by reactions with phenyl magnesium bromide and phenyl lithium, respectively.

When α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (78) was treated with phenyl magnesium bromide, the corresponding phenyl ketone (220) was obtained. This material was a liquid and formed a hydrochloride (m.p. 231-235°). Neither the base nor the hydrochloride was identical with products obtained by ZnCl_2 -acetic anhydride rearrangement



of the diol (217).

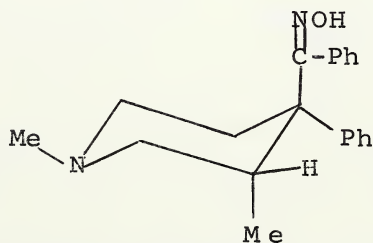
When β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (77) was treated with phenyl lithium a new compound was



obtained (m.p. 116-118^o) which was assigned the ketimine structure (221) from IR evidence and elemental analysis. This ketimine formed a dihydrochloride (m.p. 262-263^o) (the C=N band of its IR spectrum showed the characteristic base to salt shift typical of ketimines) (Hassan 1967).

When this ketimine (221) was hydrolyzed by heating with dilute hydrochloric acid, the corresponding ketone (219) was obtained which was identical with the ketone obtained by rearrangement method (IR, PMR and mixed melting point evidence). This ketone (219) formed a hydrochloride (m.p. 274-275^o) which was also identical with that of the ketone obtained by rearrangement method. On this basis, the ketone obtained from the diol (217) is assigned the β -(cis 3-Me/4-Ph) configuration (219). This result also provides good support for the cis 3-Me/4-CN configuration of the intermediate cyanohydrin (213).

Unfortunately, attempts to convert this ketone (219) into the corresponding oxime (222) under forcing



222

conditions resulted in recovery of the ketone (219) hydrochloride. Evidently, the 3-Me substituent hinders oxime formation in this derivative.

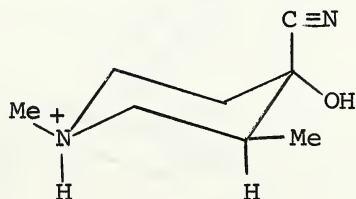
PMR CHARACTERISTICS OF PRODUCTS DERIVED FROM 1,3-DIMETHYL-4-PIPERIDONE:-

1) 1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINONITRILE:- When 1,3-dimethyl-4-piperidone was treated with KCN-HCl or acetonecyanohydrin a solid product of sharp melting point was obtained in high yield. The isomeric purity of this product is supported by the sharp nature of its PMR signals, in particular its sec. methyl doublet. This signal provides evidence that the 3-methyl group has a preferred equatorial conformation, as follows:-

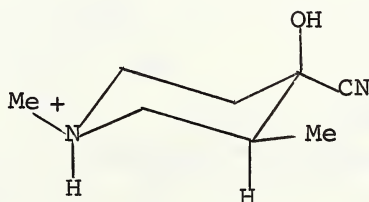
1) the sec. methyl chemical shift suffers only a small change when the base is protonated (base 59 Hz; HCl 63 Hz from TMS in DMSO-d₆).

2) the signal appearance is typical of a virtually coupled system (deformed doublet with peak separation near 5 Hz). Thus, the cyanohydrin has either the cis 3-Me/4-CN configuration (225) or the trans configuration (226).

The former is supported by knowledge of the stereochem-



225



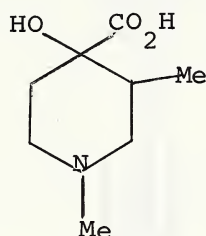
226

istry of cyanohydrin formation in 2-methylcyclohexanone (mentioned earlier) and confirmed by the chemical studies

already described.

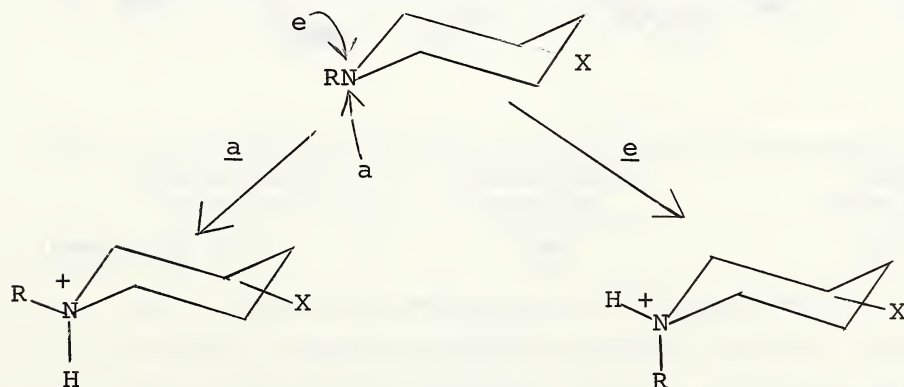
2) 1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINECARBOXYLIC ACID (204)

HYDROCHLORIDE:-



204

The unusual feature of the PMR spectrum of the acid (204) hydrochloride in DMSO- d_6 is the appearance of a pair of 3-Me doublets (Fig. 3) of about equal intensity. These demonstrate the separate existence of $N-H^+$ epimers which arise as a result of two modes (axial and equatorial) of proton uptake at the basic centres. Normally,



isomers of this nature are detected by the duplication of the N-R PMR signal and/or nearby α -substituent signals, as in the case of pseudotropine (Closs 1959) and

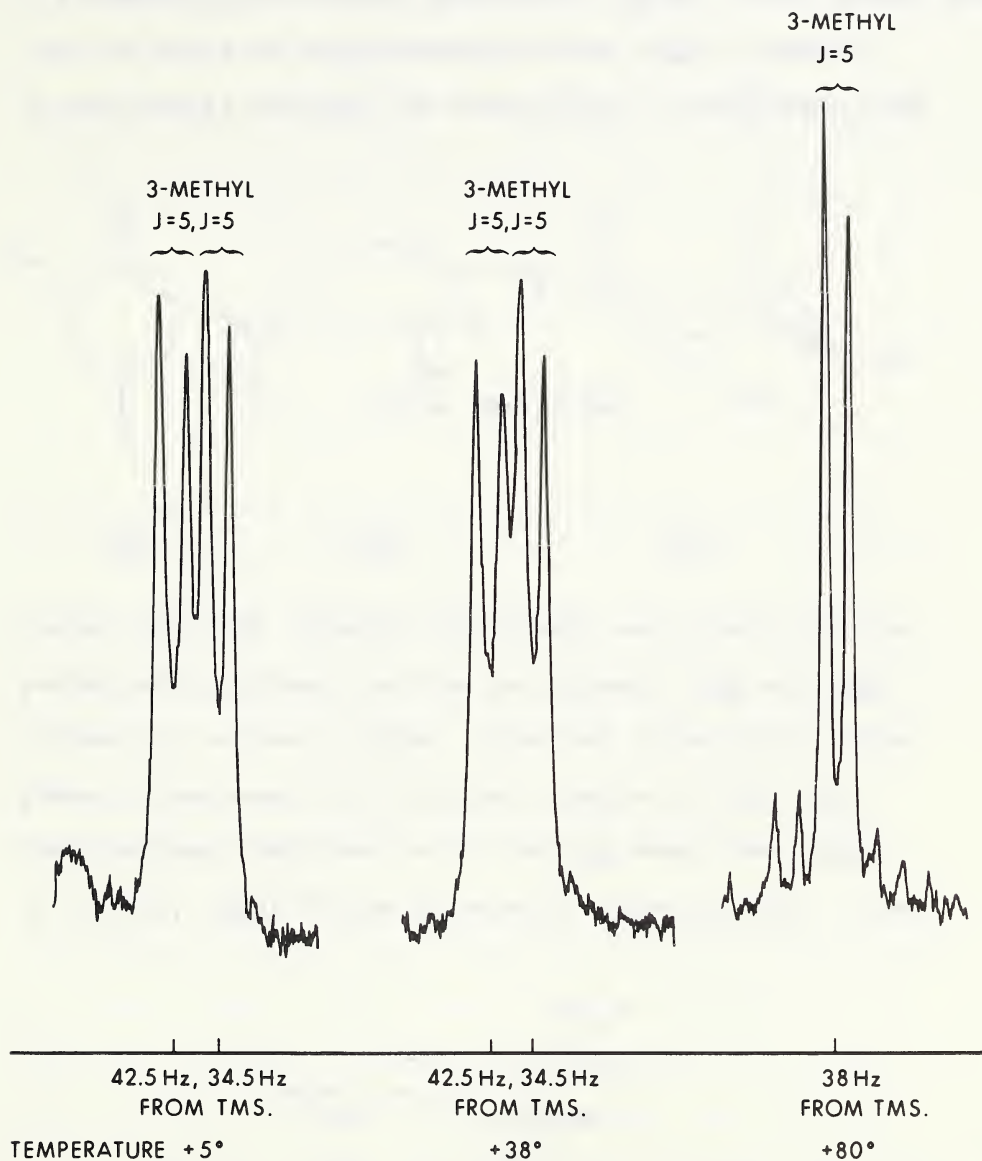
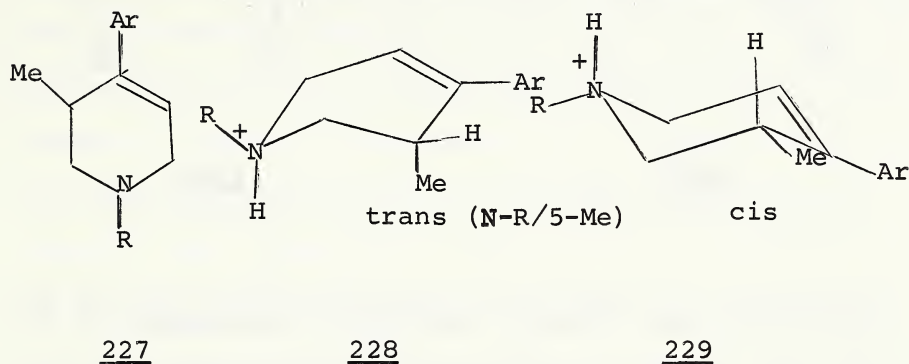
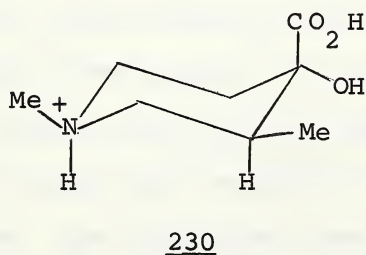


Fig. 3. Part of the PMR spectra of χ -(trans 3-Me/4-OH) 1, 3-dimethyl-4-hydroxyl-4-piperidinodiphenyl carbinol. Recorded on a Varian A-60 instrument in CDCl_3 at various temperatures.

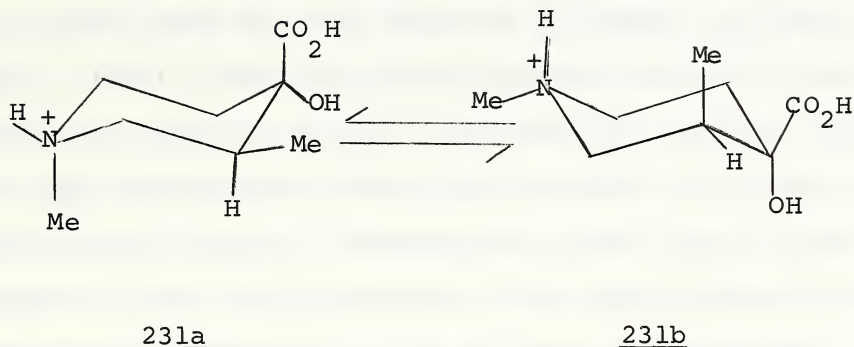
1,2-dimethylpyrrolidine (Beconsall, et.al. 1965). Epimer formation in salts of tetrahydropyridines (227), however, is manifested through the observation of duplicate C-Me



rather than N-R signals (Casy 1965) as a result of the preferred conformers of the two epimers (228 and 229) differing in 5-Me rather than N-R orientation. The present case must be a further example of this type. The favoured conformation of the cis N-Me/3-Me epimer is clearly (230) (three equatorial substituents). How-



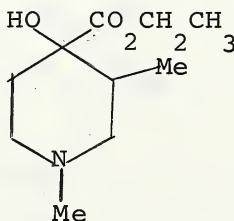
ever, both conformers of the trans epimer (231a and 231b) should be significantly populated because the same number



(2) of comparable 1,3-diaxial interactions involving the ring substituents are entailed in either form (it is assumed that the steric dimensions of OH and CO₂H do not differ greatly) (N.B. the skewboat equivalent to 231b, is also a probable conformer especially when polar solvents are used). Axial 3-Me in (231b) is deshielded by the nearly charged nitrogen atom, hence the overall chemical shift of 3-Me in the trans N-Me/3-Me epimer will be lower field than that of 3-Me in the cis epimer (230), while chemical shift differences between the epimeric N-Me groups are reduced to a point where separate signals are not observed, the N-Me signal of (204) HCl being only marginally broader than that of the free base. One unexpected feature of the N-Me signal in the hydrochloride of (204) is the absence of N-Me - N⁺-H spin-spin coupling (this would result in an N-Me doublet J=5 Hz). The N⁺-H protons must, therefore, be exchanging under the solvent conditions (DMSO-d₆) but

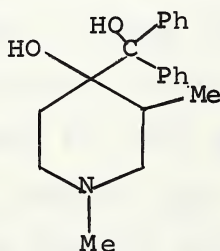
in such a way that epimeric configurations are preserved (a similar case has been reported by Menger and Mandell, 1967). When the proton exchange rate was accelerated by addition of D_2O to the $DMSO-d_6$ solution, the two sec. Me doublets moved close together to produce an approximate triplet. Temperature studies lent further support to the interpretation of the (204) hydrochloride PMR spectral characteristics in terms of protonated epimers. The separation of the two sec-Me doublets at $+5^\circ$ (5 Hz) was greater than that seen at the normal operation temperature (of about 38°) while the two doublets collapsed to one doublet which had a chemical shift intermediate between the two extremes when the temperature was raised to 80° and 90° (Fig. 3). The averaged signals seen at higher temperatures must be the result of fast proton exchange rates so that all epimers are in rapid equilibrium.

3) ETHYL 1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINOCARBOXYLATE:-

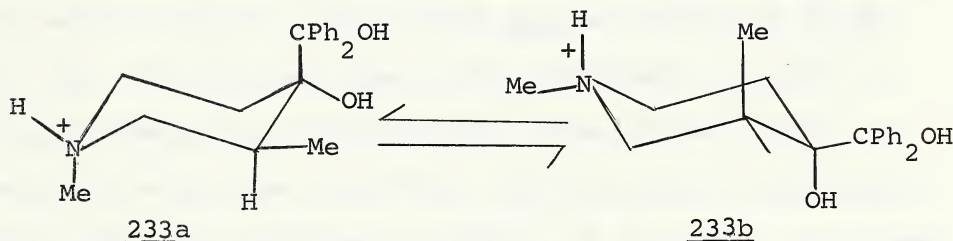
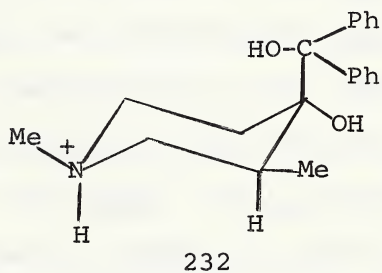


The ester (205) free base in DMSO- d_6 displayed sharp 3-Me (doublet at 51 Hz, from TMS; $J=6.5$ Hz), $CO_2 CH_2$ (quartet at 241.5 Hz; $J=7$ Hz) and $CO_2 CH_2$ Me (triplet at 70.5 Hz; $J=7$ Hz) signals in accord with its structure. All these signals were duplicated, however, in the corresponding hydrochloride spectrum (same solvent was used). This result indicates that both protonated epimers exist in DMSO- d_6 . In this case, spin-spin coupling between the NH and N-Me groups was observed, the N-Me signal being a doublet ($J=5$ Hz). When D_2O was added to the DMSO- d_6 solution, the N-Me doublet collapsed to a singlet but the 3-Me, $CO_2 CH_2$ and CO_2CH_2 Me signal still showed duplication although in less degree. Duplicate signals were also observed when the ester was examined in neat CF_3CO_2H , separations being somewhat greater than those obtained for the hydrochloride salt in DMSO- d_6 .

4) 1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINODIPHENYL CARBINOL:-

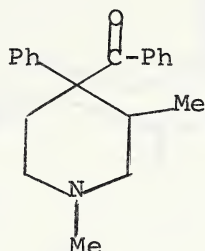


PMR spectrum of the diol (206) hydrochloride in DMSO-d_6 displayed separate signals for the two hydroxy protons (singlets at 351.5 Hz and 282 Hz from TMS, absent when $\text{NH}_3\text{-H}_2\text{O}$ added) and a single 3-Me doublet at 62 Hz, $J = 7.5$ Hz. Failure to detect two NH epimers in this example is probably due to the large difference in size between the two C-4 substituents. In this case, the cis (NMe/3Me) epimer (232) is far less stable than the trans isomer



(233b) (in the two cis chair conformations, one has the bulky CPh_2OH group axial while the other has axial N-Me, 3-Me and 4-OH features; in trans (233b) CPh_2OH is equatorial and only two 1,3-diaxial interactions (OH/H and Me/NH⁺) operate (the skewboat equivalent to 233b may also have a significant population); thus the cis population is likely to be very small. The chemical shift of the 3-Me signal in the hydrochloride salt supports the preferred axial orientation of this group (as in 233b).

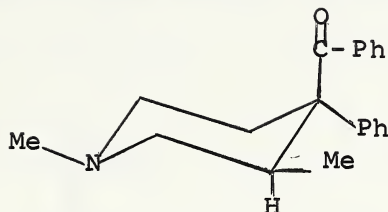
5) 1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE:-



202

PMR characteristics of the cis (3-Me/4-Ph) ketone prepared from the corresponding cis 4-cyano derivative of established configuration, were identical with those of the ketone obtained by the $\text{ZnCl}_2\text{-Ac}_2\text{O}$ induced rearrangement of the diol (206). The cis base in CDCl_3 showed two distinct aromatic singlets at 445 Hz and 437 Hz from TMS of equal intensity and a sharp sec-Me doublet at 44 Hz, $J=7$ Hz. The latter signal moved downfield to 62 Hz in the corresponding hydrochloride (same solvent used), a shift of magnitude consistent with its axial orientation. When CDCl_3 was replaced by DMSO-d_6 as a solvent, the chemical shift difference of the 3-Me group between the free base (34.5 Hz) and the hydrochloride (43.5 Hz) was reduced to 9.5 Hz. This is typical of the data obtained for β -N-substituted-3-methyl-4-phenyl-4-piperidinonitrile compounds (Table V). The β -ketimine (221) corresponding with cis ketone was readily distinguished from the ketone by its highly complex aromatic signal (CDCl_3 solvent).

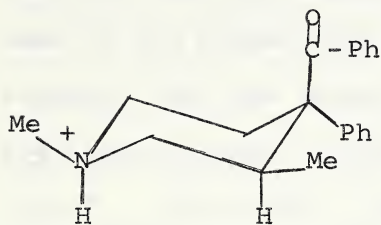
The α -ketone (234), derived from the corresponding



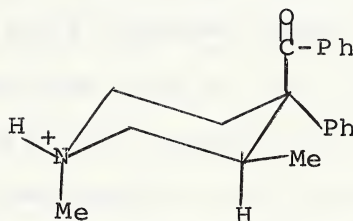
234

trans cyanide displayed a 3-Me signal with a position which was little changed when the base was protonated (base 62 Hz; HCl 62 Hz from TMS; $J=7$ Hz in CDCl_3); the lower field position of the base signal compared with the β -3-Me base chemical shift, may be attributed to the deshielding of α -Me of the α -derivative (234) by the α $\text{C}=\text{O}$ -Ph (cf. α - and β -3-Me chemical shifts values in the corresponding ethyl ketones). When the α -ketone (234) hydrochloride was examined in $\text{DMSO}-d_6$ minor (70.5 Hz) and major (56.5 Hz) sec-Me doublets were seen. Duplicate 3-Me signals were also noted when D_2O was the solvent. In this case, the lower field doublet (60.5 Hz) was almost as intense as the higher field component (49.5 Hz). These results may also be explained in terms of protonated epimers which only arise, however, when polar solvents are employed. If the steric requirements of phenyl in the vicinity of the piperidine ring are taken as much greater than those of benzoyl, the trans NMe/3Me epimer (234B) is far less favoured than the corresponding

cis epimer (234A) in the absence of molecular solvation.

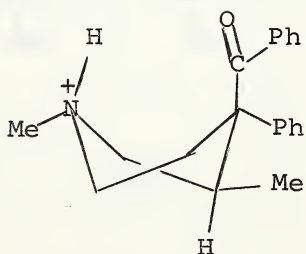


234A



234B

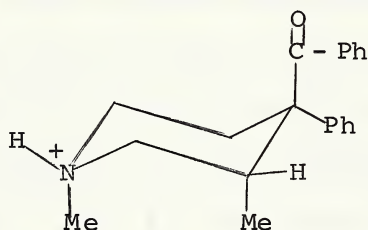
(as in CDCl_3). In polar solvents, however, the energy of (234A) will be raised by 1,3-diaxial interactions involving the solvated NH^+ and carbonyl functions. Solvation effects will also raise the energy of the chair (234B), but in this case, 1,3-interactions may be relieved by a rise in the skewboat (234c) population (the skewboats



234C

corresponding to cis chair (234A) entail either an axial N-Me group or an axial 4-phenyl group and are thus unfavoured). The net result will be to lower the energy

difference between cis and trans epimers whence both forms have comparable populations. One unexpected result is the fact that two separable epimeric 3-Me signals are seen in D_2O rather than a single averaged signal. This suggests that the proton exchange rate in the (α)-ketone 234 hydrochloride is abnormally low, possibly as a result of $C=O \cdots H-N^+$ hydrogen-bonding stabilization of the conjugate acid. pKa Measurements should confirm or otherwise, this hypothesis. No evidence of epimeric mixtures was seen in the corresponding β -ketone (202) hydrochloride in $DMSO-d_6$ (the sec-Me signal was a single doublet at 43 Hz from TMS). In this case, formation of the cis N-Me/3-Me epimer (202D) is highly unfavoured be-



202D

cause of the severe Me-Me 1,3-diaxial interactions that arise following equatorial protonation. A similar effect has also been noticed in the corresponding (α)-ethyl ketone (111) hydrochloride in D_2O .

PHARMACOLOGY:-

Most of the isomeric 3-methylpethidine analogues considered for synthesis at the outset of this work were obtained in amounts sufficient for pharmacological evaluation. These and related compounds were sent to Dr. E.L. May, Chief of the Medicinal Chemistry section of the National Institutes of Health, Bethesda, Maryland, who kindly arranged the determination of their analgesic activities in mice by the hot plate method (Eddy and Leimbach 1953; Jacobson and May 1965). A brief description of this test is given below.

Mice are placed in a cylinder on a metal plate maintained at a temperature of $55.8^{\circ} \pm 0.5^{\circ}\text{C}$. by a constant boiling mixture of ethyl formate and acetone. The animal's first sign of discomfort is to sit on its hind legs and lick or blow on its forepaws. A few seconds later, the animal kicks with the hind paws or attempts to jump out of the cylinder. Only the hind paw reaction is used for evaluation of the response time since normal mice often groom their forepaws. The criterion of the effect of an analgesic drug is the number of mice (taken in groups of 10) which do not respond within 30 seconds exposure on the hot plate.

It must be emphasized that the hot plate test does not distinguish between narcotic analgesics and other agents which have depressant effects upon the central nervous system. The tranquillizing agent haloperidol,

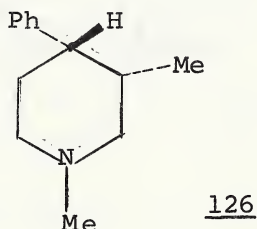
for example, has a much lower hot plate ED_{50} value in mice than has pethidine (0.84 mg./kg. compared with 28.0 mg./kg. for pethidine, Janssen and Jageneau 1956). Methods of establishing the morphine-like actions of a compound which has a hot plate ED_{50} value of the same order as, or smaller than that of pethidine, include finding out if its depressant actions are antagonized by nalorphine and comparing the potencies of N-Me and N-phenethyl analogues. In N-Me morphine-like compounds, this structure change almost invariably leads to a substantial potency rise (Eddy and Janssen 1960).

With these limitations of the hot plate test in mind, consideration of the pharmacological data available at the time of writing this thesis will now be made (Table XI).

EFFECT OF INTRODUCING A 3-Me GROUP INTO PETHIDINE:-

Both diastereoisomeric 3-methyl analogues of pethidine are more effective than the parent drug in the hot plate test. However, introduction of 3-Me cis to 4-Ph leads to an eleven-fold potency rise whereas the presence of trans 3-Me gives a compound which is only marginally more active (1.3 fold) than pethidine (Table XI, Nos. 1, 2 and 3). These results further demonstrate the superiority of cis 3-Me/4-Ph geometry over the trans arrangement in 4-phenylpiperidine analgesics and, in conjunction with the PMR solvent studies on these esters, support the postulate that the skew-

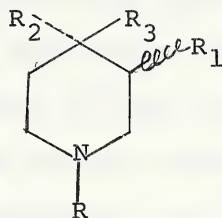
boat conformation (146) represents an optimum arrangement of structural features in analgesics of this class. It is significant in this respect that the β -analogue (126) which similarly has a skewboat conformation in

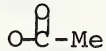
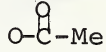
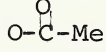


water (discussed earlier) retains half the activity of pethidine (Table XI, No. 8) even though it lacks a 4-oxygenated function previously considered an essential feature of 4-phenylpiperidine analgesics (Beckett and Casy 1965). A 4-cyano group, however, even in a cis isomer, leads to a compound of very low activity (Table XI, No. 4).

A few speculations upon reasons for the influence of a 3-methyl group upon the activity of 4-phenylpiperidine analgesics is appropriate at this stage. Although it is attractive to view 3-Me effects in terms of receptor events, due consideration should also be given to processes governing the transport and distribution of isomeric pairs. If these processes be stereoselective in any significant degree, potency difference between isomers may merely reflect differences in the ability of isomers to concentrate at the receptor rather than a difference in their receptor affinities and/or

TABLE XI. HOT-PLATE ACTIVITIES IN MICE OF SOME POLY
SUBSTITUTED PIPERIDINE COMPOUNDS AFTER SUBCU-
TANEOUS INJECTION



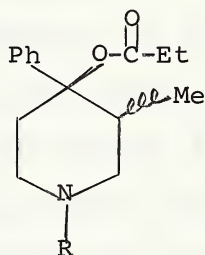
No.	Isomer and Form	R	R ₁	R ₂	R ₃	Pharmacological Activity ED ₅₀ mg./Kg.
1.	α -HCl	Me	Me	Ph	CO ₂ Et	3.60
2.	β -HCl	Me	Me	Ph	CO ₂ Et	0.42
* 3.	HCl	Me	H	Ph	CO ₂ Et	4.70
4.	β -HCl	Me	Me	Ph	C≡N	29.50
5.	HCl	Me	Me	C≡N	 -Me	8.90
6.	HCl	Me	H	C≡N	 -Me	5.06
7.	HCl	(CH ₂) ₂ Ph	H	C≡N	 -Me	6.30
8.	β -HCl	Me	Me	Ph	H	8.60

* Pethidine

intrinsic activities. This point is particularly relevant because of a recent report that brain levels of β -prodine in rats are greater than those of the α -isomer. This may be the prime factor in determining the potency difference between the prodine isomers (Portoghese and Larson 1968).

Bearing the above in mind, possible causes of activity differences between isomeric 3-methyl-4-phenylpiperidine analgesics, will now be considered.

a) Steric hindrance of the hydrolysis of 4-oxygenated functions such as OCOEt and CO₂Et (the hydrolytic products lack analgesic potencies):- This role is unlikely in view of the fact that the β -isomers of the pairs 235a and 235b are hydrolyzed somewhat more rapidly



235

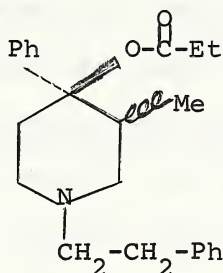
a) R=Me

b) R=(CH₂)₂Ph

than the corresponding α -isomers (Beckett and Walker 1955; Beckett et. al. 1959).

b) Influence upon the solubility properties of the drug

molecule:- A raised lipid solubility should facilitate drug penetration of lipid membranes (Albert 1965). This again appears an unlikely reason for activity differences between 3-methyl isomers. Both isomers of the



236

β - 4.4 X morphine
 α - 22.0 X morphine
 (Beckett et. al. 1959)

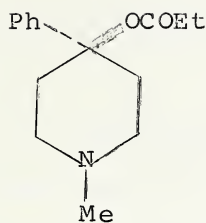
ester (236), for example, are richly endowed with lipophilic groups and it seems improbable that the 3-Me function adds significantly to this property in either isomer.

c) Creation of a difference in the base strength of an isomeric pair:- If one isomer is a weaker base than the other, the percentage of its conjugate acid will be lower at physiological pH and it should thus penetrate lipid membranes more readily than the isomer of higher pKa value (Albert 1965). Against this interpretation is the fact that the pKa values of the isomeric pair α and β -prodine do not differ significantly (α -prodine in H_2O 8.51 ± 0.04 ; β -prodine in H_2O 8.56 ± 0.06) (Casy and Pocha unpub. results).

d) Binding factors at the receptor:- It is possible

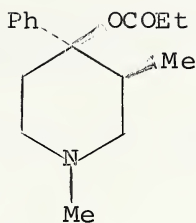
that the extra methyl group provides an additional binding site at the analgesic receptor, its placement being more effective in β -than in α -isomers. However, the potency differences between β -3-methyl isomers and the parent nor methyl compounds are usually quite significant and higher than one might anticipate through the additional binding forces (probably Van der Waals' in nature) provided by a single methyl group (polar and aromatic functions provide far stronger binding forces). Hence the activity raising action of methyl in β -isomers may be due, not to a secondary binding effect, but to the influence of this group on the conformation of the molecule. In this respect, conformational differences between α -isomer (preferred chair) and β -isomer (preferred skewboat) in water have been fully discussed already and it has been proposed that, β -methyl group leads to more effective 4-phenylpiperidine binding conformations.

It is to be noted that introduction of 3-methyl trans to phenyl in pethidine leads to only a small potency rise (Table XI, Nos. 3 and 1), while in the case of the corresponding reversed ester of pethidine, a potency fall is in fact seen (Portoghese and Larson 1968).

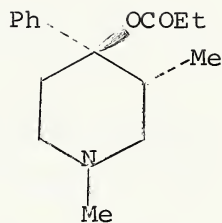


ED₅₀ 1.3 mg/Kg. α -1.7 mg/Kg.

7



237



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β -0.35 mg/Kg.

4-ACETOXY-4-PIPERIDINONITRILE DERIVATIVES:-

All three compounds tested (Table XI, Nos. 5-7) are significantly active in the hot-plate test, with two members (Table XI, Nos. 6 and 7) close to pethidine in potency. It is to be noted, however, that the N-methyl (Table XI, No. 6) is somewhat more active than the N-phenethyl analogue. This result is completely atypical of narcotic analgesics where the N-phenethyl member is usually more potent by a factor of six (Eddy and Janssen 1960). Hence the central nervous system depressant effects of these derivatives are probably brought about in a different manner to those of the narcotic analgesics. Confirmation of the narcotic-like actions of the 3-methyl pethidine isomers prepared in this thesis should derive from comparative hot-plate activities of N-Me and N-phenethyl analogues.

EXPERIMENTAL

EXPERIMENTAL

All melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 21 and Beckmann Infrared Spectrophotometer Model 10. PMR spectra were determined on Varian Associates Models A-60 and A-60D spectrometers. Elemental analyses were performed by Dr. G. Weiler and Dr. F.B. Strauss, Microanalytical Laboratories, Oxford, England and by the department of Chemistry, Microanalysis Laboratory, University of Alberta. All the chemicals obtained from commercial sources were used without further purification unless otherwise specified.

N- β -HYDROXYETHYL-N- β -HYDROXYPROPYLAMINE (57)

The title compound b.p. 121-124°/1.5 mm. was prepared by modified procedure of Cottle, et. al. (1946) by condensing 2-aminoethanol (4 mole) with propylene oxide (1 mole) (the reported ratio being 9:1).

N-p-TOSYL-2-HYDROXYETHYL-2-HYDROXYPROPYLAMINE (58)

A mixture of Na₂CO₃ (53 g.), N-2-hydroxyethyl-2-hydroxypropylamine (23.80 g.; 0.20 mole) in H₂O (300 ml.) was stirred and heated to 70°. When the solution was complete, p-tosyl chloride (41.80 g.; 0.22 mole) was added over 20 min. and the temperature raised to 95° and maintained for 2 hr. The cooled product was extracted with ether. The ether extract was dried (MgSO₄) and evaporated. The residue (50.30 g.; 92%) m.p. 68-69° was recrystallized from benzene to give the title compound, m.p. 69-70° (Janssen 1963 reported m.p. 66.2-68.2°).

IR spectrum (nujol-mull)

ν ^l max. 1350 (SO₂ asym. str.) and 1160 (SO₂ sym. str.) cm⁻¹.

Anal. calcd. for C₁₂H₁₉NSO₄ C, 52.73; H, 6.76; N, 5.09

Found: C, 52.82; H, 7.01; N, 5.12.

N-p-TOSYL-2-CHLOROETHYL-2-CHLOROPROPYLAMINE (59)

Thionyl chloride (42.48 g.; 0.36 mole) was added dropwise to N-p-tosyl-2-hydroxyethyl-2-hydroxypropylamine (24.0 g.; 0.09 mole) in chloroform (100 ml.) with stirring.

After the complete addition, the mixture was stirred at room temperature for an additional 1 hr. and then heated to reflux for 5 hr. The CHCl_3 and the unreacted thionyl chloride were removed. The residue (quantitative yield) was recrystallized from benzene m.p. 118-120°

IR spectrum (nujol-mull):-

Hydroxyl peaks (in the 3400-3100 cm^{-1} region) disappeared.

Anal. calcd. for $\text{C}_{12}\text{H}_{17}\text{NClSO}_2$ C, 46.45; H, 5.48; N, 4.85

Found: C, 46.15; H, 5.58; N, 4.52.

Note:- It is very hard to purify the title compound; and in subsequent reactions the crude product was used.

ATTEMPTED SYNTHESIS OF α -AND β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILES (61 and 60)

Phenylacetonitrile (7.02 g.; 0.06 mole) was added dropwise to a stirred suspension of NaH (6.24 g.; 0.13 mole) (50% emulsion) in benzene (100 ml.). After the completion of addition, the contents were heated to reflux for 6 hr. cooled and added N-p-tosyl-2-chlorethyl-2-chloropropylamine (10.00 g.; 0.03 mole) in benzene (150 ml.) dropwise with stirring and the reaction mixture was heated to reflux for 6 hr. cooled and decomposed with H_2O (10 ml.). The benzene layer was separated, washed with H_2O (100 ml.) and the solvent removed. The residue (13.15 g.) dissolved in MeOH (10 ml.) on shaking and deposited no solid on refrigerating for a week.

ATTEMPTED SYNTHESIS OF α - AND β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILES (61 and 60)

NaH (50% emulsion; 5.28 g.; 0.11 mole) was added in small portions to a stirred and cooled solution of N-p-tosyl-2-chloroethyl-2-chloropropylamine (16.08 g.; 0.05 mole) and phenylacetonitrile (6.08 g.; 0.05 mole) in DMF (30 ml.). After the complete addition, the mixture was brought to room temperature and then heated at 90-100° for 3 hr. After cooling, the mixture was diluted with H₂O (100 ml.). No solid or liquid separated. The mixture was then extracted with CHCl₃, filtered and the solvent removed. The residue (21.50 g.) could not be resolved into pure isomers by preferential solubility method using MeOH, ligroin, benzene, ether, etc.

ATTEMPTED SYNTHESIS OF α - AND β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILES (61 and 60)

Phenylacetonitrile (5.85 g.; 0.05 mole) in benzene (100 ml.) was added to a stirred suspension of NaNH₂ (4.29 g.; 0.11 mole) in benzene (200 ml.) with stirring. After the complete addition, the contents were heated to reflux for 8 hr. The mixture was cooled and N-p-tosyl-2-chloroethyl-2-chloropropylamine (15.00 g.; 0.05 mole) in benzene (150 ml.) added with stirring. After the complete addition, the mixture was heated to reflux for 8 hr. The reaction product was cooled, decomposed with H₂O (25 ml.) and the benzene layer separated. The benzene layer on removing the

benzene provided a residue (17.89 g.) which could not be resolved into pure isomers by MeOH, acetone, ether, CHCl_3 , etc. and by column chromatography over Al_2O_3 .

ATTEMPTED SYNTHESIS OF α - AND β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILES (61 and 60)

A mixture of N-p-tosyl-2-chloroethyl-2-chloropropylamine (13.78 g.; 0.044 mole) in toluene (200 ml.) and NaNH_2 (5.25 g.; 0.13 mole) was heated at about 45° . Phenylacetonitrile (3.79 g.; 0.03 mole) in toluene (100 ml.) was then added portionwise with stirring to control the exothermic reaction. After the complete addition, the reaction mixture was heated to reflux for 2 hr., and then stirred at room temperature for an additional 6 hr. After cooling, the mixture was decomposed with H_2O (30 ml.). The organic layer was separated and the solvent removed. The residue weighed 12.63 g.

IR spectrum (film):-

\nearrow max 3600-3100 region (NH and NH_2 str.), 2250 ($\text{C}\equiv\text{N}$ str.), 1640 ($\text{C}=\text{N}$ str.), 1345 (SO_2 asym. str.) and 1162 (SO_2 sym. str.) cm^{-1} .

Hence in addition to nitriles, there may be some amidines formed in this reaction.

The residual mixture could not be resolved into pure nitrile and/or amidine components by preferential solubility method using MeOH as a solvent.

SYNTHESIS OF α - AND β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILES (61 and 60)

A mixture of N-p-tosyl-2-chloroethyl-2-chloropropylamine (27.00 g.; 0.09 mole) in toluene (150 ml.) and NaNH_2 (8.97 g.; 0.23 mole) was cooled to about 5° . Phenylacetonitrile (10.53 g.; 0.09 mole) in toluene (100 ml.) was added to the above mixture with stirring. The resultant mixture was allowed to assume the room temperature, heated to reflux for 3 hr. and then stirred at room temperature for 8 hr. The cooled mixture was decomposed with H_2O (30 ml.) and filtered. The residue (6.08 g.) was boiled with MeOH (50 ml.), filtered and the residue washed with MeOH thrice. The residue (3.35 g.; m.p. $215-216^\circ$) on recrystallization from n-butanol melted at $217-218^\circ$ (Janssen 1963 reported m.p. $217.5-218.5^\circ$ for the β -isomer).

Infrared spectrum (nujol-mull):-

\checkmark max 2210 ($\text{C}\equiv\text{N}$ str.) cm^{-1} .

The toluene layer was separated from the filtrate and the residue obtained by evaporation of the solvent was chromatographed over Al_2O_3 . Fractions 6 and 7 (wt. 4.52 g.; elution with CH_2Cl_2) afforded crude α -isomer which on recrystallization from MeOH melted at $149-149.5^\circ$ (Janssen 1963 reported m.p. $146.5-149^\circ$).

IR spectrum (nujol-mull):-

\checkmark max 2220 ($\text{C}\equiv\text{N}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{SO}_2$ C, 67.76; H, 6.25

Found: C, 67.75; H, 6.16.

N, O, O-TRITOSYL-N-2-HYDROXYETHYL-N-2-HYDROXYPROPYLAMINE (67)

To a cooled solution of p-tosyl chloride (14.25 g.; 0.075 mole) in pyridine (30 ml.), was added with shaking N-p-tosyl-2-hydroxyethyl-2-hydroxypropylamine (10.00 g.; 0.037 mole). The mixture was shaken well and refrigerated at 10° for 72 hr. At the end of this time, the reaction mixture was poured into chilled 2NHCl (250 ml.) and extracted with ether. The ether layer was dried (anhy. Na₂SO₄) and evaporated. The residue (17.60 g.; 84%) was purified by column chromatography over alumina. Fraction 1 (elution with benzene; quantitative recovery) afforded the title compound.

IR spectrum (film):

✓ max 1370-1330 (SO₂ asym. str.) and 1200-1150 (SO₂ sym. str.) cm⁻¹. Hydroxyl bands (3400-3200 cm⁻¹ region) present in the starting material disappeared.

Anal. calcd. for C₂₆H₃₁NS₃O₈ N, 2.41.

Found: N, 2.59.

N, O, O-TRITOSYL-N-2-HYDROXYETHYL-N-2-HYDROXYPROPYLAMINE

(67)

To a cooled solution of p-tosyl chloride (117.80 g.; 0.62 mole), in pyridine (300 ml.) was added N-2-hydroxyethyl-N-2-hydroxypropylamine (23.80 g.; 0.20 mole). The reaction mixture was shaken well and refrigerated at 10° for 72 hr. At the end of this time, the mixture was

poured into chilled 6NHCl (800 ml.) and extracted with benzene. The residue (91.00 g.; 80%) obtained on evaporation of benzene was a thick syrupy liquid.

Infrared spectrum (film)

IR spectrum of this material was identical with the same compound (67) obtained by a two step method.

α - AND β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINO-NITRILES (61 and 60)

A solution of phenylacetonitrile (93.60 g.; 0.80 mole) in tetrahydrofuran (150 ml.) was added over 1 hr. to a suspension of NaNH₂ (24.98; 0.64 mole) in tetrahydrofuran (50 ml.). After the complete addition, a solution of N, O,O-tritosyl-N-2-hydroxyethyl-N-2-hydroxypropylame (90.00 g.; 0.15 mole) in tetrahydrofuran (150 ml.) was added over 30 min. The reaction mixture was then heated to reflux for 28 hr. The cooled mixture was treated with NH₄Cl (30 g.) followed by H₂O (50 ml.). The residue obtained on evaporation of the solvent was taken up in H₂O (200 ml.) and the organic material extracted with CHCl₃. The CHCl₃ layer was dried and evaporated. The residue was taken up in MeOH (100 ml.), heated to boiling and filtered. The residue (10.60 g.; 20%) melted at 214-216° (Janssen 1963 reported m.p. 217.5-218.5 for the β -isomer).

Infrared spectrum (nujol-mull) was identical with that of the β -isomer prepared previously.

The MeOH filtrate was evaporated and unreacted phenyl-

acetonitrile removed (by distillation under reduced pressure) from the filtrate. The residue (15.70 g.; 29%) on recrystallization from MeOH melted at 148-149° (Janssen 1963 reported m.p. 146.5-149° for the α -isomer).

IR spectrum (nujol-mull) was identical with that of the α -isomer prepared previously.

N-2-CHLOROETHYL-N-2-CHLOROPROPYLAMINE (73)

The title compound b.p. 78-80°/8 mm. was obtained from the corresponding dihydroxy compound according to the procedure of Idson and Spoerri (1954). It formed a hydrochloride in acetone m.p. 203-205° (Arnold 1961 reported m.p. 207° for the hydrochloride).

ATTEMPTED PREPARATION OF α -AND β -3-METHYL-4-PHENYL-4-PIPERIDINONITRILES

NaNH_2 (6.24 g.; 0.16 mole) was added in small portions to a solution of 2-chloroethyl-2-chloropropylamine (10.00 g.; 0.060 mole) and phenylacetonitrile (8.19 g.; 0.08 mole) in toluene (150 ml.). The temperature was maintained below 25° during the addition. The mixture was heated to reflux for 2 hr. and then stirred at room temperature for an additional 8 hr. The mixture was hydrolyzed with H_2O (10 ml.) and extracted with dil. HCl solution (10%). The aqueous portion was basified with NaOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (14.10 g.) was a dark brown thick syrupy liquid.

IR spectrum (film):-

ν_{\max} 2220 (C \equiv N str.), 1635 (C=N str.) cm^{-1} .

The residue was converted into its hydrochloride but all attempts to resolve the mixture into pure components by preferential solubility method were unrewarding (MeOH, acetone, benzene, ether, petroleum ether tried).

The residue (8.40 g.; free base) was chromatographed over Al_2O_3 . No sizeable fraction was obtained with characteristic IR spectrum indicative of the desired product(s).

N-METHYL-2-HYDROXYETHYL-2-HYDROXYPROPYLAMINE (74)

N-2-Hydroxyethyl-N-2-hydroxypropylamine (23.80 g.; 0.20 mole) was added to cooled 88% HCO_2H (60.00 g; 1.20 mole) with shaking. Formaldehyde 37% (54 ml.; 0.67 mole) was added to the resulting clear solution. The mixture was shaken well and heated to reflux for 10 hr. The cooled mixture was basified strongly with KOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue was distilled under reduced pressure to give the title compound (22.75 g.; 85%), b.p. 100-102°/1.75 mm. (Jones and Wilson 1949 reported b.p. 127°/16 mm.).

It formed a picrate which on recrystallization from ethyl acetate melted at 72-73° (Jones and Wilson 1949 reported m.p. 71-72°).

N-METHYL-2-CHLOROETHYL-2-CHLOROPROPYLAMINE (75) HYDRO-
CHLORIDE

Thionyl chloride (90.00 g.; 0.76 mole) in CHCl_3 (100 ml.) was added dropwise to a stirred solution of N-methyl-2-hydroxyethyl-2-hydroxypropylamine (21.30 g.; 0.16 mole) in CHCl_3 (150 ml.). After the completion of addition, the contents were refluxed for 4 hr. The CHCl_3 and the unreacted thionyl chloride were removed and the residue was dried by azeotropic distillation with benzene. The residue (34.40 g.; 96%) on recrystallization from acetone melted at $112-113^\circ$.

IR spectrum (nujol-mull):-

\checkmark max 2750-2150 cm^{-1} (NH). Hydroxyl bands (3600-3200 cm^{-1} region) disappeared.

Anal. calcd. for $\text{C}_6\text{H}_{13}\text{NCl}_2 \cdot \text{HCl}$ C, 34.89; H, 6.77.

Found: C, 34.84; H, 6.68.

α - AND β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE
(78) and (77) HYDROCHLORIDES

Phenylacetone nitrile (58.50 g.; 0.50 mole), N-methyl-2-chloroethyl-2-chloropropylamine (72.00 g.; 0.42 mole) and dry toluene (500 ml.) were mixed together and NaNH_2 (48.75 g.; 1.25 mole) was added in small portions with stirring and external cooling. During this addition, the temperature of the mixture was maintained between $5-10^\circ$. After the complete addition, the mixture was brought to room temperature slowly and then refluxed for 4 hr. The

cooled mixture was hydrolyzed with H_2O (30 ml.) and extracted with 15% HCl (400 ml.). The aqueous layer was basified with NaOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue weighed 83.40 g.

The aqueous layer was also extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated. The residue (9.80 g.) appeared to be a mixture of amide and/or amidines (\checkmark max. 1670 and 1630 cm^{-1}). All attempts to resolve the mixture by hydrochloride formation and subsequent preferential solubility method were unsuccessful.

SEPARATION OF α - AND β -ISOMERS (78 and 77) FROM THE ETHER EXTRACT

The ether extract was treated with acetone-HCl to give the hydrochlorides. Acetone insoluble isomer (22.50 g.; 21%) on recrystallization from absolute ethanol melted at 275-276° and was assigned the β -cis (3-Me/4-Ph) configuration (77) on the basis of PMR data (discussed earlier). IR spectrum (nujol-mull):

\checkmark max 2800-2300 (NH^+), 2230 ($\text{C}\equiv\text{N}$ str.); 1600 (phenyl gr.) and 690 (monosubs. benzene ring) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\cdot\text{HCl}$ C, 67.05; H, 7.63; N, 11.17
Found: C, 67.35, H, 7.62; N, 10.92.

When no further β -isomer separated on concentrating the acetone portion, the remaining acetone was evaporated.

The residue was dissolved in ethyl acetate by heating, cooled to room temperature and allowed to stand in the refrigerator over night. The solid which separated was isolated by filtration. The residue (70.00 g.; 67%) on recrystallization from ethyl acetate melted at 205°-206° and was assigned the α -trans (3-Me/4-Ph) configuration (78) on the basis of PMR data.

IR spectrum (nujol-mull)

ν_{max} 2750-2300 (NH^+), 2220 ($\text{C}\equiv\text{N}$ str.), 1600 (phenyl group) and 690 (monosubst. benzene) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\cdot\text{HCl}$ C, 67.05; H, 7.63; N, 11.17.

Found: C, 66.91; H, 7.43; N, 10.97.

ATTEMPTED PREPARATION OF α AND β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE ISOMERS (78 and 77)

Phenylacetonitrile (70.2 g.; 0.60 mole), N-methyl-2-chloroethyl-2-chloropropylamine (84.00 g.; 0.50 mole) and toluene (500 ml.) were mixed together and NaNH_2 (62.40 g.; 1.60 mole) was added in small portions with stirring and maintaining the temperature between 10-27°. The mixture was allowed to assume the room temperature and then heated to reflux for 5 hr. The cooled mixture was hydrolyzed with H_2O (40 ml.) and extracted with 15% HCl solution (400 ml.). The aqueous layer was basified with NaOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (87.70 g.) on shaking with dry ether deposited a solid

(15.80 g.) which on recrystallization from benzene melted at 137-138°.

The aqueous portion was extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated. The residue (34.30 g.) on washing with ether afforded a solid (20.50 g.) which on recrystallization from benzene melted at 137-138°. This compound was assigned α -1,3-dimethyl-4-phenyl-4-piperidinocarboxamidine (79) on the basis of PMR data, and elemental analyses.

PMR spectrum (Hz from TMS in CDCl_3 at 60 MHz):

445 Hz main peak of multiplet (5 aryl protons); 293 Hz singlet (3 amine protons); 155-108 Hz (10 protons due to N-methyl and piperidine ring protons) and 75.5 Hz (3-methyl protons).

IR spectrum (nujol-mull):-

✓ max 3500-3200 region (NH and NH_2 str.), 1630 ($\text{C}=\text{N}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{21}\text{N}_3$ C, 72.68; H, 9.15; N, 18.16.

Found: C, 72.37; H, 9.07; N, 17.97.

This substance formed a dihydrochloride monohydrate which on recrystallization melted at 255-257°.

IR spectrum (nujol-mull):

✓ max 1670 ($\text{C}-\overset{+}{\text{N}}(\text{H})-\text{H}$) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{21}\text{N}_3 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$ C, 52.17; H, 7.77; N, 13.04.

Found: C, 52.23; H, 7.52; N, 13.15.

α -AND β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILES
(78) AND (77)

A solution of phenylacetonitrile (58.50 g.; 0.50 mole) in toluene (100 ml.) was added slowly to a cooled mixture of N-methyl-2-chloroethyl-2-chloropropylamine (55.00 g.; 0.32 mole) and NaNH_2 (39.00 g.; 1.00 mole). The mixture was allowed to stand at room temperature over night and then heated to reflux for 4 hr. The mixture was decomposed with H_2O (30 ml.) and extracted with 20% HCl solution (200 ml.). The aqueous portion was basified with NaOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue weighed 58.00 g.

The aqueous portion was also extracted the CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated. The residue weighed 26.00 g.

The ether extract was treated with acetone- HCl . The separation of the two isomers was accomplished at this stage. The material insoluble in acetone (24.30 g.; 30%) on recrystallization from ethanol melted at $275\text{--}276^\circ$ and was assigned the β -configuration (77) IR spectrum (nujol-mull) was identical with that of the β -isomer prepared previously.

The acetone soluble portion (14.44 g.; 18%) on recrystallization from ethyl acetate melted at $204\text{--}206^\circ$ (previously found m.p. $205\text{--}206^\circ$). This isomer was assigned the α -configuration (78).

IR spectrum (nujol-mull) was identical with that of the

α -isomer obtained previously.

CHCl₃ EXTRACT:- The residue was taken up in ether, shaken well and filtered. The filtrate on concentrating to approximately 50 ml. and cooling deposited a solid (100 mg.) which on washing with ether melted at 191-193°. This compound was assigned the structure β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamidine (80).

IR spectrum (nujol-mull)

ν^{max} 3400-3100 (NH and NH₂ str.) and 1680 (C=N) cm⁻¹.

Anal. calcd. for C₁₄H₂₁N₃ C, 72.68; H, 9.15; N, 18.16.

Found: C, 72.53; H, 9.05; N, 17.93.

N-BENZYL-2-HYDROXYETHYL-2-HYDROXYPROPYLAMINE (81)

A mixture of NaHCO₃ (33.60 g.), H₂O (100 ml.), N-2-hydroxyethyl-N-2-hydroxypropylamine (31.20 g.; 0.26 mole) was heated to about 90-95° to affect the complete solution and benzyl chloride (36.96 g.; 0.29 mole) was added in about 1 hr. with stirring. The temperature was maintained at 90° for 4 hr. The cooled mixture was extracted with ether. The ether layer was extracted with 20% HCl solution (150 ml.). The aqueous portion was basified strongly with NaOH (solid) and the basic material extracted with ether. The ether layer was dried (anhy. K₂CO₃) and evaporated. The residue was distilled under reduced pressure to give the title compound (45.98 g.; 76%) b.p. 156-160°/1 mm.

Anal. Calcd. for $C_{12}H_{19}NO_2$ C, 68.90; H, 9.09; N, 6.69.

Found: C, 68.78; H, 9.13; N, 6.77.

N-BENZYL-2-CHLOROETHYL-2-CHLOROPROPYLAMINE (82)

Thionyl chloride (89.68 g.; 0.76 mole) in dry $CHCl_3$ (100 ml.) was added dropwise to a stirred solution of N-benzyl-2-hydroxyethyl-2-hydroxypropylamine (39.65 g.; 0.19 mole) and the mixture heated to reflux for 4 hr. The residue obtained, on evaporation of the solvent and the unreacted thionyl chloride, was dissolved in H_2O (50 ml.), basified with NH_4OH solution and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue was distilled under reduced pressure to yield the title compound (22.00 g.; 47%) b.p. $123-127^\circ/1.5$ mm.

Anal. calcd. for $C_{12}H_{17}NCl_2$ C, 58.78; H, 6.94; N, 5.71.

Found: C, 58.88; H, 7.37; N, 6.00.

β -N-BENZYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (83)

Phenylacetone nitrile (9.36 g.; 0.08 mole), N-benzyl-2-chloroethyl-2-chloropropylamine (20.00 g.; 0.081 mole) and toluene (250 ml.) were mixed together and $NaNH_2$ (7.80 g.; 0.20 mole) was added in small portions with stirring and cooling. During this addition, the temperature of the mixture was maintained between $10-20^\circ$. The mixture was heated to reflux for 1 hr. and stirred at room temperature for an additional 12 hr. The cooled reaction mixture was extracted with 10% HCl solution

(150 ml.). The aqueous portion was basified with NH_4OH and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (18.20 g.) was taken up in acetone and acetone saturated with hydrogen chloride was added to it; followed by ether addition. The addition of ether continued until no more liquid separated. The solvent portion was decanted. The residue could not be resolved into pure components by preferential solubility method.

However, the decanted ether-acetone portion on keeping at room temperature deposited a solid (2.71 g.; 10%) which on recrystallization from ethanol melted at $235.5\text{--}236.5^\circ$. This isomer was assigned the β -cis(3-Me/4-Ph) configuration on the basis of PMR data and chemical correlation with β -1,3-dimethyl-4-phenyl-4-piperidinonitrile.

IR spectrum (nujol-mull):-

ν_{max} 2750-2300 $^+$ (NH), 2220 ($\text{C}\equiv\text{N}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\cdot\text{HCl}$ C, 73.50; H, 7.04; N, 8.57.

Found: C, 73.30; H, 6.68; N, 8.51.

ATTEMPTED ESTERIFICATION OF β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE (77) HYDROCHLORIDE

β -1,3-Dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (2.50 g.; 0.01 mole) and conc. HCl (10 ml.) were heated to reflux for 20 hr. The H_2O and excess HCl were removed and the residue was dried by azeotropic distillation with benzene. Absolute ethanol (20 ml.) and conc.

H_2SO_4 (2 ml.) were added to the above residue and the mixture heated under reflux for 12 hr. A portion of the solvent (15 ml.) was removed, the residue basified with NH_4OH solution and the basic material extracted with CHCl_3 . This layer was dried (anhy. MgSO_4) and evaporated. The residue (1.80 g.) exhibited bands at 2210 ($\text{C}\equiv\text{N}$ str.), 1710 ($\text{C}=\text{O}-\text{OEt}$), 1670 ($\text{C}=\text{NH}_2$ str.) cm^{-1} . The residue was dissolved in benzene and allowed to stand in the refrigerator over night. A solid was deposited which on recrystallization from benzene melted at $160-161^\circ$.

IR spectrum (CHCl_3)

ν_{max} 3400-3300 (NH_2 str.); 1670 ($\text{C}=\text{O}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$ C, 72.41; H, 8.64; N, 12.07.

Found: C, 72.38; H, 8.94; N, 11.90.

IR spectrum and elemental analyses showed that this compound was β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamide (90).

ATTEMPTED ESTERIFICATION OF β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE (77) HYDROCHLORIDE

A mixture of β -1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (1.99 g.; 0.008 mole), 95.5% H_2SO_4 (6.60 g.) and H_2O (2 ml.) was heated at $110-120^\circ$ for 3 hr. The mixture was cooled to room temperature, ethanol (15 ml.) added and the contents refluxed for 16 hr. The excess ethanol was removed, the residue basified (with sat. Na_2CO_3 solution) and the basic material extracted

with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (1.39 g.) on recrystallization from benzene melted at $158-159^\circ$. IR spectrum (in $CHCl_3$) of this material was identical with that of the β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamide obtained previously. No depression in melting point was observed when a mixed melting point of this material and an authentic sample of the amide (90) was determined.

The material formed a hydrochloride m.p. $265-267^\circ$ in acetone.

Anal. calcd. for $C_{14}H_{20}N_2O \cdot HCl$ C, 62.69; H, 7.83; N, 10.44.
Found: C, 62.40; H, 8.38; N, 10.21.

ATTEMPTED HYDROLYSIS OF β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE (77) HYDROCHLORIDE

A mixture of β -1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (1.00 g.; 0.004 mole), conc. H_2SO_4 (9.50 ml.) and H_2O (0.50 ml.) was heated at 120° for 8 hr. The cooled mixture was diluted with water (10 ml.), basified with 40% KOH solution and extracted with ether. The ether layer was dried (anhy. K_2CO_3), and evaporated. The residue (155 mg.) on recrystallization from benzene melted at $155-158^\circ$. This material was assigned β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamide (90) on the basis of identical IR spectra and mixed melting point with the authentic sample.

The aqueous portion was acidified strongly with dil. HCl (20%) solution and the excess HCl and H_2O were re-

moved. The dried residue (dried by azeotropic distillation with benzene) was extracted with boiling ethanol, filtered and the solvent removed from the filtrate. The residue (618 mg.) on recrystallization from ethanol melted at 300-301.5°.

AgNO₃ test and BaCl₂ test positive.

IR spectrum (nujol-mull):-

3600-3150 (OH str.) 2800-2400 (⁺NH), 1670 ($\overset{\text{O}}{\parallel}\text{C}$ str.) cm⁻¹.

Anal. calcd. for C₁₄H₁₉NO₂·H₂SO₄ C, 50.75; H, 6.34; N, 4.23.

Found: C, 50.49; H, 6.65; N, 7.41.

ATTEMPTED HYDROLYSIS OF α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE (78) HYDROCHLORIDE

A mixture of α -1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (5.00 g.; 0.02 mole); conc. H₂SO₄ (40 ml.) and H₂O (2 ml.) was heated at 120° for 10 hr. The cooled mixture was diluted with H₂O (50 ml.), basified with 40% KOH solution and extracted with ether. The ether layer was dried (anhy. K₂CO₃) and evaporated. The residue (730 mg.) melted at a very long range. It formed a crude hydrochloride (m.p. 125-220°) which could not be purified by recrystallization using acetone.

IR spectrum (nujol-mull):-

\checkmark max 3260 and 3100 (NH₂ str.), 2700-2400 (⁺NH), 1700, 1670 ($\overset{\text{O}}{\parallel}\text{C}$ str.) cm⁻¹.

The aqueous portion was acidified strongly with conc. HCl. The excess HCl and H₂O were removed and the residue

was freed from traces of H_2O by azeotropic distillation with benzene. The residue (5.06 g.) was a grey solid. This material appeared to be a mixture of hydrogen chloride and hydrogen sulphate salts (m.p. 70-150°) as shown by $AgNO_3$ and $BaCl_2$ tests respectively.

ATTEMPTED HYDROLYSIS OF β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE (77) HYDROCHLORIDE

A mixture of β -1,3-dimethyl-4-phenyl-4-piperidinonitrile hydrochloride (4.64 g.; 0.018 mole), KOH (6.72 g.; 0.12 mole) and ethylene glycol (60 ml.) was heated at 170° for 15 hr. The ethylene glycol was distilled off. The residue was taken up in H_2O (20 ml.) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (1.59 g.) on recrystallization from benzene melted at 160-161° and was identical with the authentic sample of β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamide (IR and mixed m.p. evidence).

The aqueous portion was acidified strongly with 20% HCl solution. The excess HCl and H_2O were removed and the residue was freed from traces of H_2O by azeotropic distillation with benzene. The residue was extracted with ethanol, filtered and the ethanol removed from the filtrate. The residue on shaking with acetone afforded a solid (426 mg.) which did not melt up to 300°. Ignition test:- This material burns with a smoky flame. Infrared spectrum (nujol-mull):-

✓ max. 3600-3100 (OH str.), 2750-2400 (NH), 1785, 1710 +

and 1670 (δ str.) cm^{-1} .

ATTEMPTED HYDROLYSIS OF α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINONITRILE (78)

A mixture of α -1,3-dimethyl-4-phenyl-4-piperidino-nitrile (4.24 g.; 0.019 mole), KOH (6.72 g.; 0.12 mole) and ethylene glycol (60 ml.) was heated at 170° for 9 hr. The cooled mixture was acidified with 20% HCl solution (30 ml.) and ethylene glycol and H_2O were removed by distillation under reduced pressure. The dried residue (dried by azeotropic distillation with benzene) was extracted with ethanol, filtered and the filtrate evaporated. The residue (a thick syrupy liquid) was taken up in H_2O (25 ml.) and basified with 10% NaOH solution. The basic material was extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated to yield a residue (3.42 g.).

IR spectrum (in CHCl_3):-

\checkmark max 3500-3100 (NH_2 str.); 2220 ($\text{C}\equiv\text{N}$ str. in traces), 1720 ($\text{C}=\text{O}$ str. of ester in traces); 1670 ($\text{C}=\text{O}$ str. of the amide; major) cm^{-1} .

All attempts to isolate one or all of the components in pure form from free base of crude hydrochloride of (m.p. 70 - 180°) of the mixture were unsuccessful.

The aqueous portion was acidified with 20% HCl solution. The excess HCl and H_2O were removed. The dried residue (freed from traces of H_2O by azeotropic distillation with benzene) was a thick brown liquid and could not

be converted into pure α -1,3-dimethyl-4-phenyl-4-piperidinocarboxylic acid (93) hydrochloride.

ATTEMPTED HYDROLYSIS OF β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOCARBOXAMIDE (90)

A mixture of β -1,3-dimethyl-4-phenyl-4-piperidinocarboxamide (0.61 g.) and 30% NaOH solution (15 ml.) was refluxed for 16 hr. and then allowed to stand at room temperature for 24 hr. The basic material was extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (0.44 g.) melted at $159-160.5^\circ$. IR spectrum of this compound was identical with that of the starting material.

ATTEMPTED HYDROLYSIS OF α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOCARBOXAMIDINE (79)

A mixture of α -1,3-dimethyl-4-phenyl-4-piperidinocarboxamidine (4.62 g.; 0.02 mole) and dil. HCl solution (20 ml. conc. HCl + 60 ml. H_2O) was heated to reflux for 8 hr. The cooled mixture was basified with NaOH (solid) and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (anhy. K_2CO_3) and evaporated. The residue on washing once with ether weighed 3.72 g. and melted at $135-136^\circ$ (m.p. of starting material $137-138^\circ$). IR spectrum (nujol-mull) of this material was identical with that of the starting material.

ATTEMPTED HYDROLYSIS OF α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOAMIDINE (79)

A mixture of α -1,3-dimethyl-4-phenyl-4-piperidino-carboxamidine (2.80 g.; 0.012 mole) and conc. HCl (20 ml.) was heated at 150° for 7 hr. and then at 200° for 3 hr. The cooled mixture was basified with 20% NaOH solution and extracted with CHCl₃. The CHCl₃ layer was dried (anhy. K₂CO₃) and evaporated. The residue on washing with anhy. ether weighed 2.24 g. and melted at 135-136.5° (m.p. of starting material 137-138°). IR spectrum of this material was identical with that of the starting material.

ATTEMPTED HYDROLYSIS OF α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOCARBOXAMIDINE (79)

A mixture of α -1,3-dimethyl-4-phenyl-4-piperidino-carboxamidine (3.00 g.; 0.013 mole), KOH solid (2.91 g.; 0.052 mole) and 95% C₂H₅OH (30 ml.) was heated to reflux for 10 hr. The solvent was evaporated and the residue diluted with H₂O (15 ml.). The basic mixture was extracted with CHCl₃. The CHCl₃ layer was dried (anhy. K₂CO₃) and evaporated. The residue (2.81 g.) melted at 134-135° (m.p. and mixed m.p. with the starting material 137-138°). IR spectrum (nujol-mull) of this material was identical with that of the starting material.

β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLIC
ACID (99)

A mixture of β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (1.97 g.; 0.0056 mole), solid KOH (2.00 g.; 0.035 mole) and ethylene glycol (20 ml.) was heated at 170° for 9 hr. The cooled mixture was diluted with H₂O (20 ml.) acidified with 20% HCl solution and filtered. The residue was washed with H₂O and dried by azeotropic distillation with benzene. The residue (2.25 g.; quantitative yield provided the sample has 1 mole of H₂O) on recrystallization from absolute ethanol melted at 210° (Janssen 1963 reported m.p. 208.5-210.5°).

IR spectrum (nujol-mull):-

✓ max. 3420-3200 region (OH str.), 1700 (C^O str.), 1355 (SO₂ asym. str.), 1165 (SO₂ sym. str.) cm⁻¹. Nitrile band (2220 cm⁻¹) disappeared.

Anal. calcd. for C₂₀H₂₃NSO₄· $\frac{1}{2}$ H₂O C, 62.81; H, 6.33; N, 3.66;
Found: C, 62.77; H, 6.33; N, 3.69.

α -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLIC
ACID (100)

A mixture of α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinonitrile (11.45 g.; 0.032 mole), solid KOH (14.00 g.; 0.25 mole) and ethylene glycol (150 ml.) was refluxed for 24 hr. The cooled mixture was diluted with H₂O (100 ml.) acidified with 20% HCl solution and filtered. The dried residue (12.20 g.; 100%) on recrystallization from eth-

anol melted at 192.5-194.5° (Janssen 1963 reported m.p. 173.4-175.8°).

IR spectrum (nujol-mull):-

✓ max 3500-3240 region (OH str.), 1710 (C=O str.), 1360 (SO₂ asym. str.) and 1180 (SO₂ sym. str.) cm⁻¹.

Anal. calcd. for C₂₀H₂₃NSO₄ C, 64.34; H, 6.17.

Found: C, 64.01; H, 6.41.

ETHYL β-N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE (101)

A mixture of β-N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylic acid monohydrate (2.50 g.; 0.0064 mole) and thionyl chloride (30 ml.) was stirred at room temperature until a clear solution was obtained (12 hr.). The unreacted thionyl chloride was evaporated. Absolute ethanol (30 ml.) was added to the residue and the mixture refluxed for 8 hr. The residue (926 mg; 37%); obtained on evaporation of the ethanol, on recrystallization from absolute ethanol melted at 109.5-110.5° (Janssen 1961 reported m.p. 102-104.6°).

IR spectrum (nujol-mull):-

✓ max. 1725 (C=O str.), 1350 (SO₂ asym. str.) and 1165 (SO₂ sym. str.) cm⁻¹. OH bands (3420-3200 cm⁻¹) present in the starting material disappeared.

Anal. calcd. for C₂₂H₂₇NSO₄ C, 65.83; H, 6.73; N, 3.49.

Found: C, 65.73; H, 7.06; N, 3.56.

ETHYL α -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINOCAR-
BOXYLATE (102)

A mixture of α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylic acid (12.20 g.; 0.033 mole) and thionyl chloride (50 ml.) was refluxed for 12 hr. The unreacted thionyl chloride was removed and absolute ethanol (100 ml.) added to the residue and the mixture refluxed for 8 hr. The residue (10.00 g.; 77%), obtained on evaporation of the ethanol, on recrystallization from ethanol melted at 127-128° (Janssen 1961 reported m.p. 127.8-128.2°).

IR spectrum (nujol-mull):-

$\sqrt{}$ max. 1725 (C=O str.), 1360 (SO₂ asym. str.) and 1160 (SO₂ sym. str.) cm⁻¹. Hydroxyl bands (3500-3240 cm⁻¹ region) present in the starting material disappeared.

Anal. calcd. for C₂₂H₂₇NSO₄ C, 65.83; H, 6.73.

Found: C, 65.72; H, 6.89.

ETHYL β -3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE (104)

A mixture of ethyl β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylate (2.90 g.; 0.0072 mole), phenol (5.00 g.; 0.053 mole) and 30% HBr solution in acetic acid (20 ml.) was heated at 110° for 6 hr. with occasional shaking and then stirred at room temperature for 18 hr. Ether (100 ml.) was added and the reaction product extracted with H₂O (75 ml.). The aqueous portion was basified with 40% KOH solution and extracted with ether. The

ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (1.51 g.; 85%) was a thick yellow liquid.

IR spectrum (film):-

✓ max. 3500-3200 broad (NH str.); 1730 (C=O str.) cm^{-1} .
Bands at 1350 (SO_2 asym. str.) and 1165 (SO_2 sym. str.) cm^{-1} disappeared.

N.B. The crude material was used in the subsequent reactions without purification.

ETHYL α -3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE (105)

A mixture of ethyl α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinocarboxylate (6.64 g.; 0.017 mole), phenol (10.00 g.; 0.11 mole) and 30% HBr solution in acetic acid (30 ml.) was heated at 110° for 8 hr. with occasional shaking and then allowed to stand at room temperature over night. Ether (100 ml.) was added and the reaction product extracted with H_2O (100 ml.). The aqueous layer was basified with 40% KOH solution and extracted with ether. The ether portion was dried (anhy. K_2CO_3) and evaporated. The residue (3.25 g.; 80%) was a light yellow liquid.

IR spectrum (film):-

✓ max 3500-3100 broad (NH str.), 1720 (C=O str.) cm^{-1} .

N.B. The crude material was used in the subsequent reactions without further purification.

ETHYL β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE
(106)

A mixture of ethyl β -3-methyl-4-phenyl-4-piperidinocarboxylate (1.33 g.; 0.005 mole), 37% HCHO (5 ml.) and 88% HCO₂H (5 ml.) was refluxed for 6 hr. The cooled mixture was diluted with H₂O (10 ml.), basified with 40% KOH solution and extracted with ether. The ether portion was dried (anhy. K₂CO₃) and evaporated. The residue (1.38 g.; 99%) was a light yellow liquid. This material formed a hydrochloride in ether which on recrystallization from benzene melted at 182-183° (Jansen 1963 reported m.p. 181-182°).

IR spectrum (nujol-mull)

$\nu_{\text{max.}}$ 2700-2200 (NH)⁺, 1725 (C=O str.) cm⁻¹.

Anal. calcd. for C₁₆H₂₃NO₂·HCl C, 64.64; H, 8.08.

Found: C, 64.40; H, 8.02.

ETHYL α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE
(107)

A mixture of ethyl α -3-methyl-4-phenyl-4-piperidinocarboxylate (1.00 g.; 0.004 mole), 37% HCHO (5 ml.) and 88% HCO₂H (5 ml.) was refluxed for 6 hr. The cooled mixture was diluted with H₂O (10 ml.), basified with 40% KOH solution and extracted with ether. The ether extract was dried (anhy. K₂CO₃) and evaporated. The residue (1.00 g.; 94%) was a light yellow liquid. This material formed a hydrochloride in ether which on recrystallization

from ethyl acetate melted at 168-169° (Janssen 1963 reported m.p. 168-169°).

IR spectrum (nujol-mull):-

✓ max 2700-2200 ($\overset{+}{\text{NH}}$), 1730 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{HCl}$ C, 64.64; H, 8.08.

Found: C, 64.84; H, 8.37.

ETHYL β -N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE (108):-

A mixture of ethyl β -3-methyl-4-phenyl-4-piperidinocarboxylate (1.23 g.; 0.005 mole), anhy. Na_2CO_3 (5.00 g.), 2-bromoethylbenzene (1.11 g.; 0.006 mole) and n-BuOH (20 ml.) was refluxed for 24 hr. with stirring. The cooled mixture was filtered and the solvent removed from the filtrate by distillation under reduced pressure. The residue formed a hydrochloride (1.71 g.; 89%) which on recrystallization from acetone melted at 212°.

IR spectrum (nujol-mull):-

✓ max 2800-2200 ($\overset{+}{\text{NH}}$), 1720 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_2\cdot\text{HCl}$ C, 71.31; H, 7.75; N, 3.61.

Found: C, 71.50; H, 7.48; N, 3.88.

ETHYL α -N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOCARBOXYLATE (109)

A mixture of ethyl α -3-methyl-4-phenyl-4-piperidinocarboxylate (1.00 g.; 0.004 mole), anhy. Na_2CO_3 (5.00 g.), 2-bromoethylbenzene (1.11 g.; 0.006 mole) and n-BuOH (20 ml.) was refluxed for 24 hr. The reaction mixture was

filtered and the solvent removed from the filtrate by distillation under reduced pressure. The residue (1.54 g.; 98%) formed a hydrochloride in ether which on recrystallization from ethanol-ether melted at 176-177°.

IR spectrum (nujol-mull):-

ν_{max} 2700-2100 (NH)⁺, 1720 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{23}\text{H}_{29}\text{NO}_2 \cdot \text{HCl}$ C, 71.31; H, 7.75; N, 3.61

Found: C, 71.05; H, 7.93; N, 3.67.

However, when the above reaction was repeated with crude starting material, in addition to the ester (109) a small amount of ethyl- α -N-phenethyl-3-methyl-4-phenyl-4-piperidinocarboxamide (110) hydrochloride (90 mg.) melting at 231-235° was obtained.

IR spectrum (nujol-mull):-

ν_{max} 2700-2100 (NH)⁺, 1720 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O} \cdot \text{HCl}$ C, 70.39; H, 7.54; N, 7.82.

Found: C, 70.69; H, 7.35; N, 7.38.

α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE (111)

Ethyl bromide (21.80 g.; 0.20 mole) in dry ether (100 ml.) was added with vigorous stirring to Mg turnings (3.65 g.; 0.15 mole) in dry ether (100 ml.) and a crystal of iodine. After the complete addition, the contents were refluxed for 10 hr. The reaction mixture was cooled to room temperature and α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (10.20 g.; 0.05 mole) in toluene (150 ml.) added dropwise with stirring. After the addition was

complete, the ether was removed by distillation and the residue refluxed for 10 hr. The cooled mixture was hydrolyzed with 10% HCl solution. The aqueous layer was separated and the toluene layer extracted with 10% HCl solution. The combined aqueous portion was basified with NaOH (solid) and the basic material extracted with ether. The ether portion was dried (anhy. K_2CO_3) and evaporated. The residue (10.35 g.) was a dark brown viscous oil.

IR spectrum (film):-

✓ max. 1710 (C=O str.), 1635 (C=N) cm^{-1} . Nitrile band (2220 cm^{-1}) disappeared.

The residue was heated on a steam bath with 10% HCl solution (80 ml.) for 8 hr., basified with NaOH (solid) and extracted the product with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue was distilled under reduced pressure to yield the desired ketone (111) (7.59 g.; 60%) b.p. 160-170°/2 mm.

IR spectrum (film):-

✓ max. 1700 (C=O str.) cm^{-1} . C=N band (1635 cm^{-1}) disappeared.

Anal. calcd. for $C_{16}H_{23}NO$ C, 78.36; H, 9.39;

Found: C, 78.50; H, 9.32.

All attempts to convert this material to a corresponding hydrochloride, hydrobromide and/or oxalate were unsuccessful.

β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE (113)

Ethyl bromide (8.72 g.; 0.08 mole) in ether (100 ml.) was added to Mg. turnings (1.46 g.; 0.06 mole) in ether (100 ml.) and a crystal of iodine with vigorous stirring and the reaction mixture refluxed for 10 hr. β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (4.80 g.; 0.022 mole) in toluene (100 ml.) was added to the cooled mixture. The ether was removed by distillation and the contents refluxed for 18 hr. The cooled mixture was hydrolyzed with 10% HCl solution. The aqueous portion was separated and the toluene layer extracted with 10% HCl solution. The combined aqueous portion was basified and the product extracted with ether. The ether portion was dried (anhy. K_2CO_3) and evaporated. The residue (3.64 g.) was a dark brown liquid.

IR spectrum (film):-

ν_{\max} 1705 (C=O str.), 1625 (C=N str.) cm^{-1} . Nitrile band ($2220\ cm^{-1}$) present in the starting material disappeared.

The residue was heated on a steam bath with 10% HCl solution (25 ml.) for 12 hr., basified with 40% NaOH solution and extracted the basic material with ether. The ether portion was dried (anhy. K_2CO_3) and evaporated to afford the desired ketone (3.38 g.; 64%).

IR spectrum (film):-

ν_{\max} 1705 (C=O str.). C=N band ($1625\ cm^{-1}$) disappeared.

This ketone (113) formed a hydrochloride in ether which on recrystallization from acetone melted at $238-242^\circ$.

IR spectrum (nujol-mull):-

ν_{max} 2750-2200 (NH), 1710 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{16}\text{H}_{23}\text{NO} \cdot \text{HCl}$ C, 68.33; H, 8.54; N, 4.98.

Found: C, 68.33; H, 8.42; N, 4.50.

β -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE

(117)

Ethyl bromide (8.72 g.; 0.08 mole) in ether (100 ml.) was added to magnesium turnings (1.46 g.; 0.06 mole) and a crystal of iodine in ether (100 ml.) with vigorous stirring and the reaction mixture was refluxed for 10 hr.

β -N-p-Tosyl-3-methyl-4-phenyl-4-piperidinonitrile (7.08 g.; 0.02 mole) in toluene (150 ml.) was added to the above reaction mixture with cooling. The ether was removed by distillation and the remainder refluxed for 10 hr. The cooled reaction mixture was hydrolyzed with 10% HCl solution (60 ml.). The toluene layer was separated and the aqueous layer extracted with CHCl_3 . The combined toluene and CHCl_3 portion was dried (anhy. MgSO_4) and the solvents removed by distillation under reduced pressure. The residue (7.02 g.) was a light yellow solid (m.p. 80-140°) and was a mixture of the desired ketone (117) and the corresponding ketimine (118) and the starting material.

IR spectrum (nujol-mull):-

ν_{max} 2220 ($\text{C}\equiv\text{N}$ str.), 1680 (C=O str.); 1630 (C=N str.) cm^{-1} .

β -3-METHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE (119)

A mixture of β -N-p-tosyl-3-methyl-4-phenyl-4-piperidinoethyl ketone and the corresponding ketimine (5.40 g.) phenol (10.00 g.) and 30% HBr solution in acetic acid (30 ml.) was heated at 110° for 5 hr. The reaction mixture was allowed to stand at room temperature over night. Ether (100 ml.) was added to the above mixture and extracted with H_2O (50 ml.). The aqueous layer was basified with 50% KOH solution and extracted with ether. The ether extract was dried (anhy. K_2CO_3) and evaporated. The residue (2.25 g.) was a light yellow liquid and was a mixture of the desired ketone (119) and the corresponding ketimine (120).

IR spectrum (film)

\checkmark max 3400-3200 broad (N-H str.), 1705 (C=O str.), 1630 (C=N str.) cm^{-1} .

A portion of above mixture (1.20 g.) was heated with 10% HCl solution (20 ml.) for 6 hr. on a steam bath. The cooled mixture was basified with 40% NaOH solution and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated to provide the title compound (0.84 g.)

IR spectrum (film)

\checkmark max 3400-3200 broad (N-H str.), 1703 (C=O str.) cm^{-1} .

β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE (113)

A mixture of β -3-methyl-4-phenyl-4-piperidinoethyl

ketone (1.00 g.; 0.004 mole), 37% HCHO solution (5 ml.) and 88% HCO₂H (5 ml.) was refluxed for 6 hr. The cooled mixture was diluted with H₂O (10 ml.), basified with 40% KOH solution and extracted with ether. The ether extract was dried (anhy. K₂CO₃) and evaporated to afford the title compound (113) (1.04 g.; 98%) which was a light yellow liquid. It formed a hydrochloride in ether which on recrystallization from acetone melted at 241-243° (mixed m.p. with the authentic sample 241-243°).

Infrared spectrum of this material was identical with that of the authentic sample.

β-N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOETHYL
KETONE (121)

A mixture of β-3-methyl-4-phenyl-4-piperidinoethyl ketone (750 mg.; 0.0032 mole); anhy. Na₂CO₃ (5.00 g.), 2-bromoethylbenzene (1.11 g.; 0.006 mole) and n-BuOH (20 ml.) was refluxed for 24 hr. The mixture was filtered and the residue washed twice with n-BuOH. The solvent was removed from the filtrate. The residue was dissolved in ether (50 ml.) and filtered. The filtrate was dried (anhy. K₂CO₃) and evaporated to afford the title compound (121) (1.07 g.; 100%).

IR spectrum (nujol-mull)

✓ max. 1700 (C=O str.) cm⁻¹. N-H band (3400-3200 cm⁻¹) present in the starting material disappeared.

This material formed a hydrochloride in ether which on recrystallization from acetone melted at 244-246°.

Anal. calcd. for $C_{23}H_{29}NO \cdot HCl$ C, 74.55; H, 8.09; N, 3.77.

Found: C, 74.58; H, 7.92; N, 4.06.

α -N-p-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE

Ethyl bromide (8.72 g.; 0.08 mole) in ether (100 ml.) was added to magnesium turnings (1.46 g.; 0.06 mole) and crystal of iodine in ether (100 ml.) with vigorous stirring and the reaction mixture was refluxed for 10 hr. α -N-p-Tosyl-3-methyl-4-phenyl-4-piperidinonitrile (7.08 g.; 0.02 mole) in toluene (150 ml.) was added to the above reaction mixture with external cooling. The ether was removed by distillation and the remainder refluxed for 10 hr. The cooled reaction was hydrolyzed with 10% HCl solution (60 ml.). The toluene layer was separated and the aqueous layer extracted with $CHCl_3$. The combined toluene and $CHCl_3$ portion was dried (anhy. $MgSO_4$) and the solvents removed by distillation under reduced pressure. The residue (7.00 g.) was a sticky solid and could not be recrystallized from MeOH and/or ether. This material was used as such in the subsequent reactions without purification.

α -3-METHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE

A mixture of α -N-p-tosyl-3-methyl-4-phenyl-4-piperidinoethyl ketone and the corresponding ketimine (7.00 g.), phenol (10 g.) and 30% HBr solution in acetic acid (30 ml.) was heated at 110° for 5 hr. The reaction mixture was allowed to stand at room temperature over-

night. Ether (100 ml.) was added to the above mixture and the basic material was extracted with H_2O (50 ml.). The aqueous layer was basified with KOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (3.20 g.) was a mixture of the desired ketone, the corresponding ketimine and the corresponding nitrile.

IR spectrum (film):-

✓ max 3400-3200 broad (N-H str.), 2220 ($C\equiv N$ str.), 1702 ($C=O$ str.), 1630 ($C=N$ str.) cm^{-1} .

The above residue (3.10 g.) was heated with 10% HCl solution (30 ml.) for 6 hr. on a steam bath. The cooled mixture was basified with 40% NaOH solution and the liberated basic material was extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (2.71 g.) was a liquid and a mixture of the title compound and the corresponding nitrile.

IR spectrum (film):-

✓ max. 3400-3200 broad (N-H str.), 2210 ($C\equiv N$ str.), 1705 ($C=O$ str.) cm^{-1} . 1630 ($C=N$ str.) cm^{-1} band disappeared.

✓ -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE (111)

A mixture of Δ -3-methyl-4-phenyl-4-piperidinoethyl ketone and the corresponding nitrile (1.013 g.), 37% HCHO solution (5 ml.) and 88% HCO_2H (5 ml.) was refluxed for 6 hr. The cooled mixture was diluted with H_2O

(10 ml.), basified with 40% KOH solution and the liberated base was extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated to afford the title compound and its corresponding nitrile (1.515 g.) which was a light yellow liquid.

IR spectrum (film):-

ν_{\max} 2220 (C \equiv N str.), 1710 (C=O str.) cm^{-1} .

The residue (1.50 g.) was chromatographed over alumina. Fractions 3 and 4 (elution with benzene afforded the title compound (111).

IR spectrum of this material was identical with that of the authentic sample prepared previously by an independent method.

ATTEMPTED SYNTHESIS OF α -N-PHENETHYL-3-METHYL-4-PHENYL-4-PIPERIDINOETHYL KETONE

A mixture of α -3-methyl-4-phenyl-4-piperidinoethyl ketone and its corresponding nitrile (1.50 g.), anhy. Na_2CO_3 (10.00 g.), 2-bromoethylbenzene (2.40 g.) and n-BuOH (40 ml.) was refluxed for 24 hr. The mixture was filtered when hot and the residue washed twice with warm n-BuOH. The solvent was removed from the filtrate. This residue was dissolved in ether (100 ml.), dried (anhy. K_2CO_3) and the solvent evaporated. The residue (2.05 g.) was a mixture of the desired ketone and the corresponding nitrile.

IR spectrum (film):-

ν_{\max} 2220 (C \equiv N str.), 1705 (C=O str.) cm^{-1} . 3400-

3200 broad (NH str.) cm^{-1} band disappeared.

This material formed a hydrochloride in ether which on recrystallization from acetone weighed 0.47 g. and melted at $249-251^{\circ}$. This material is α -N-phenethyl-3-methyl-4-phenyl-4-piperidinonitrile (122) as shown by IR spectrum (nujol-mull) and elemental analyses.

IR spectrum (nujol-mull):-

ν_{max} 2700-2250 $^{+}$ (NH), 2220 ($\text{C}\equiv\text{N}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_2\cdot\text{HCl}$ C, 73.17; H, 7.62; N, 8.53.

Found: C, 73.00; H, 7.41; N, 8.47.

All attempts to obtain the hydrochloride of the desired ketone in crystalline form were unrewarding.

HYDROGENOLYSIS OF β -N-BENZYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (83) HYDROCHLORIDE

A mixture of β -N-benzyl-3-methyl-4-phenyl-4-piperidinonitrile hydrochloride (3.00 g.; 0.0089 mole), 10% palladized charcoal (0.60 g.) and 95% ethanol (100 ml.) was stirred with hydrogen at room temperature until no further hydrogen gas was absorbed (uptake 400 ml.). The mixture was filtered and the solvent removed from the filtrate. The residue (1.90 g.; 91%) on recrystallization from a MeOH-ether solvent system melted at $220-221^{\circ}$.

This was shown to be β -3-methyl-4-phenyl-4-piperidinonitrile (103) hydrochloride on the basis of IR spectrum and elemental analyses.

IR spectrum (nujol-mull):-

ν_{max} 3600-2300 bands $^{+}$ (N-H), 2220 ($\text{C}\equiv\text{N}$ str.) cm^{-1} .

Anal. calcd. for $C_{13}H_{16}N_2 \cdot HCl$ C, 66.10; H, 7.20; N, 11.83.
Found: C, 65.89; H, 7.19; N, 11.52.

β -N-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (60)

A mixture of dry Na_2CO_3 (1.00 g.), H_2O (10 ml.) and β -3-methyl-4-phenyl-4-piperidinonitrile hydrochloride (0.81 g.; 0.0034 mole) was heated to 70° to affect the complete solution. *p*-Tosyl chloride (0.68 g.; 0.0036 mole) was added and the temperature raised to 95° and maintained at that temperature for about 1.5 hr. The cooled mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried (anhy. $MgSO_4$) and evaporated. The residue (1.10 g.; 91%) on recrystallization from *n*-BuOH melted at $217-218^\circ$ (Janssen 1963 reported m.p. $217.5-218.5^\circ$).

ATTEMPTED DETOSYLATION OF β -N-*p*-TOSYL-3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (60)

β -N-*p*-Tosyl-3-methyl-4-phenyl-4-piperidinonitrile (4.77 g.; 0.013 mole), phenol (5.00 g.; 0.053 mole) and 30% HBr solution in acetic acid (25 ml.) was stirred at room temperature for 20 hr. Ether (100 ml.) was added and the precipitated solid separated by filtration. The residue on washing twice with ether (20 ml. portions) and drying provided the starting material (3.93 g.; 82%) m.p. $217-218^\circ$. IR spectrum (nujol-mull) was identical with that of the authentic sample.

β -3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (103)

A mixture of N-*p*-tosyl-3-methyl-4-phenyl-4-piperi-

dinonitrile (3.90 g.; 0.011 mole); phenol (5.00 g.; 0.053 mole), and 30% HBr solution in acetic acid (25 ml.) was heated to 110° slowly to affect a complete solution and then heated to reflux for 4 hr. The mixture was then stirred at room temperature for 36 hr. Ether (100 ml.) was added and the reaction product extracted with H_2O (70 ml.). The aqueous portion was basified with 20% KOH solution and extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated to afford a mixture (2.00 g.) of the desired nitrile and the corresponding amide.

IR spectrum (nujol-mull):-

ν_{max} 3320-3100 bands (N-H str. and NH_2 str.); 2220 ($\text{C}\equiv\text{N}$ str.), 1670 ($\text{C}=\text{O}$ str.) cm^{-1} .

SEPARATION OF β -3-METHYL-4-PHENYL-4-PIPERIDINOCARBOX-AMIDE (125)

The above residue was taken up in acetone (15 ml.), shook well and filtered. The residue (0.12 g.) melted at 191 - 192° and was shown to be β -3-methyl-4-phenyl-4-piperidinocarboxamide on the basis of IR spectrum and elemental analyses (Janssen 1962 reported m.p. 191 - 192°).

IR spectrum (nujol-mull):-

ν_{max} . 3420-3100 bands (N-H and NH_2 str.), 1675 ($\text{C}=\text{O}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ C, 71.56; H, 8.26; N, 12.84.

Found: C, 71.33; H, 8.17; N, 12.82.

SEPARATION OF β -3-METHYL-4-PHENYL-4-PIPERIDINONITRILE
(103)

The acetone portion (filtrate) formed a hydrochloride which on recrystallization from MeOH-ether weighed 1.35 g. and melted at 218-220° (mixed melting point with authentic sample showed no depression). IR spectrum (nujol-mull) of this compound was identical with that of the authentic sample prepared previously by an independent method.

β -N-CYANO-3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (124)

Cyanogen bromide (2.23 g.; 0.02 mole) in CHCl_3 (30 ml.) was added to β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (4.08 g.; 0.019 mole) in CHCl_3 (40 ml.) with stirring. After the complete addition, the mixture was stirred for an addition hr. and then heated to reflux for 4 hr. The residue obtained on evaporation of CHCl_3 was extracted with ether. The ether portion, on concentration and cooling provided (0.97 g.) of the title compound which on recrystallization from ether melted at 126-126.5°.

IR spectrum (nujol-mull)

ν_{max} . 2200 ($\text{N-C}\equiv\text{N}$ str.; v. sharp) cm^{-1} .

Anal. calcd for $\text{C}_{14}\text{H}_{15}\text{N}_3$ C, 74.66; H, 6.66; N, 18.66.

Found: C, 74.52; H, 6.59; N, 18.46.

β -3-METHYL-4-PHENYL-4-PIPERIDINONITRILE (103)

A mixture of β -N-cyano-3-methyl-4-phenyl-4-piperidinonitrile (0.62 g.; 0.0027 mole) and 10% HCl solution

(15 ml.) was heated under reflux for 12 hr. The cooled mixture was extracted with ether (to remove any non-basic material present). The aqueous portion was basified strongly (with 10% KOH solution and extracted with ether). This ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (0.47 g.) formed a hydrochloride m.p. 217-219° from acetone. (Melting point of authentic sample 218-220°). IR spectrum (nujol-mull) was identical with that of the authentic sample.

ATTEMPTED PREPARATION OF α -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOCARBOXAMIDINE (79)

A mixture of α -1,3-dimethyl-4-phenyl-4-piperidinonitrile (2.21 g.; 0.01 mole), $NaNH_2$ (3.90 g.; 0.10 mole) and toluene (100 ml.) was stirred at room temperature for 48 hr. The excess of $NaNH_2$ was decomposed with H_2O (20 ml.) and the toluene layer separated. The combined toluene layer was extracted with 20% HCl solution (100 ml.). The aqueous layer was basified with 40% KOH solution and extracted with $CHCl_3$. The $CHCl_3$ layer was dried (anhy. K_2CO_3) and evaporated. The residue (2.06 g.) was the starting material as shown by identical infrared spectra (film).

β -1,3-DIMETHYL-4-PHENYLPYPERIDINE (126)

A solution of β -1,3-dimethyl-4-phenyl-4-piperidinonitrile (2.95 g.; 0.014 mole) in toluene (50 ml.) was added dropwise to a stirred suspension of $NaNH_2$ (5.80 g.;

0.15 mole) in refluxing toluene (50 ml.). The reaction mixture was stirred and refluxed for 8 hr. The unreacted NaNH_2 was decomposed with H_2O (20 ml.). The aqueous portion was separated and the toluene layer was extracted with dil.HCl (70 ml.). The aqueous extract was basified with 20% NaOH solution and the basic material extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (2.32 g.; 86%) was the title compound (126).

IR spectrum (film):-

$\text{C}\equiv\text{N}$ band (2220 cm^{-1}) disappeared. No $\text{C}=\text{N}$ band (1640 cm^{-1}) characteristic of amidines appeared.

This material (126) formed a hydrochloride in acetone which on recrystallization from ethanol-ether melted at $237\text{-}238^\circ$ (McErlane & Casy, unpub. results reported m.p. 241°).

No depression in melting point was observed on determining mixed m.p. with the authentic sample and the infrared spectra of this material was indistinguishable from that of the authentic sample.

χ -1,3-DIMETHYL-4-PHENYLPYPERIDINE (127)

A solution of χ -1,3-dimethyl-4-phenyl-4-piperidino-nitrile (3.10 g.; 0.00145 mole) in toluene (50 ml.) was added dropwise to a well-stirred suspension of NaNH_2 (5.85 g.; 0.15 mole) in toluene (50 ml.). The contents were then refluxed for 8 hr. The unreacted NaNH_2 was

decomposed with H_2O . The toluene layer was extracted with dil. HCl solution. The aqueous extract was basified strongly with 20% NaOH solution and extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated to afford the title compound (2.54 g.; 90%) which was a light yellow liquid.

IR spectrum (film):-

$\text{C}\equiv\text{N}$ band (2220 cm^{-1}) disappeared. No band characteristic of amidines (1640 cm^{-1}) appeared.

This compound formed a hydrochloride m.p. $232-235^\circ$ from EtOH-ether.

Anal. calcd. for $\text{C}_{13}\text{H}_{19}\text{N}.\text{HCl}$ C, 69.16; H, 8.93; N, 6.22.
Found: C, 68.89; H, 9.22; N, 6.34.

It also formed a methiodide which on recrystallization from acetone softened at $143-146^\circ$.

Anal. calcd. for $\text{C}_{13}\text{H}_{19}\text{N}.\text{CH}_3\text{I}$ C, 50.76; H, 6.64; N, 4.22.
Found: C, 51.04; H, 6.50; N, 4.20.

ATTEMPTED PREPARATION OF ~~X~~-1,3-DIMETHYL-4-PHENYLPIPERIDINE (127)

~~X~~-1,3-Dimethyl-4-phenyl-4-piperidinocarboxamidine (4.62 g.; 0.02 mole) in toluene (50 ml.) was added dropwise to a suspension of NaNH_2 (7.80 g.; 0.20 mole) in boiling toluene (50 ml.). The reaction mixture was refluxed for 8 hr. and then stirred at room temperature over night. The unreacted NaNH_2 was decomposed with H_2O (25 ml.) and the separated toluene layer was extracted

with 20% HCl solution. The aqueous extract was basified with 40% KOH solution and extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated to yield 1.96 g. of the starting material (m.p. and mixed m.p. $134.5\text{--}135.5^\circ$). Infrared spectrum (nujol-mull) was identical with that of the starting material.

N-METHYLISONIPECOTIC ACID (159) HYDROCHLORIDE

Isonipecotic acid (12.90 g.; 0.10 mole) was added to 88% HCO_2H (30 g.; 0.60 mole) slowly with external cooling and shaking, 37% HCHO solution (27 ml., 0.33 mole) was added and the contents heated at $95\text{--}100^\circ$ for 10 hr. 20% HCl solution was added to the cooled mixture and the excess HCl and H_2O removed on the flash evaporator. The residue was dried by azeotropic distillation with benzene. The residue on washing with acetone thrice provided the title compound (16.94 g.; 95%) in pure form, m.p. 225° (Clarke et. al. 1949 reported m.p. $223\text{--}225^\circ$).

N-METHYLISONIPECOTIC ACID (159)

N-Methylisonipecotic acid was prepared from the corresponding hydrochloride by means of an exchange technique using Rexyn RG-1 as exchange resin and ethanol as eluant. The free base, thus obtained was purified by sublimation, m.p. $172\text{--}173^\circ$.

IR spectrum (nujol-mull) of this compound was identical with that of the authentic sample

N-METHYLISONIPECOTIC ACID (159) HYDROFORMATE

Isonipecotic acid (12.90 g.; 0.10 mole) was added with shaking and external cooling to 88% HCO_2H (30.00 g.; 0.58 mole) and 37% HCHO solution (27 ml. 0.33 mole) was added to the clear resulting solution. The contents were heated at $100-110^\circ$ for 8 hr. and excess reagents and H_2O removed using a flash evaporator. The residue was freed from traces of H_2O by azeotropic distillation with benzene. The residue on shaking thoroughly with acetone (200 ml.) and refrigerating for 10 hr. deposited a crystalline solid (15.0 g.; 80%), m.p. $87-88^\circ$.

IR spectrum (nujol-mull):-

\checkmark max 2750-2100 $^+$ (N-H); 1720 (C=O str.), 1600-1500 band (HCO_2^-) cm^{-1} .

Anal. calcd. for $\text{C}_7\text{H}_{13}\text{NO}_2 \cdot \text{HCO}_2\text{H}$ C, 50.79; H, 7.94; N, 7.41.
Found: C, 50.68; H, 7.97; N, 7.52.

N-METHYLISONIPECOTIC ACID (159)

A mixture of Pd-charcoal (3.00 g.), isonipecotic acid (12.90 g.; 0.10 mole), 37% HCHO solution (15 ml.; 0.18 mole) and 95% EtOH (100 ml.) was reduced by passing hydrogen gas (2240 ml.) with shaking. Pd-charcoal was added in two lots (3.00 g. total) during the reaction. The reaction mixture was filtered and the solvent and the unreacted HCHO removed. The residue (13.03 g.; 80%) on recrystallization provided a mono-

hydrate of the title compound; m.p. 171-172.5°.

Anal. calcd. for $C_7H_{13}NO_2 \cdot H_2O$ C, 52.17; H, 9.31; N, 8.69.

Found: C, 52.25; H, 8.92; N, 8.59.

A portion of the above sample was sublimed (140°/1 mm. for 4 hr.) to provide an anhydrous sample, m.p. 173.5-175° (previously found 172-173°). Hydroxyl band in the IR spectrum (nujol-mull) was sharper than in the corresponding monohydrate.

Anal. calcd. for $C_7H_{13}NO_2$ C, 58.74; H, 9.09.

Found: C, 58.80; H, 8.76.

LITHIUM SAND

A mixture of Li metal (2.59; 0.37 mole), paraffin oil (60 ml.) and oleic acid (2 drops, added to avoid coalescing) were heated in a flask to 240°. The heating was stopped and the mixture stirred for a few min. After cooling to room temperature, the ground lithium was removed from the top with spoon spatula and washed with ether.

N-METHYL-4-BENZOYLPIPERIDINE (165)

A solution of bromobenzene (12.56; 0.08 mole) in ether (80 ml.) was added dropwise with stirring to a suspension of Li sand (prepared from 1.12 g.; 0.16 mole Li metal) in ether (60 ml.). and refluxed for 5 hr. N-Methylisonipecotic acid (5.0 g.; 0.035 mole) was suspended in ether (100 ml.) and phenyl lithium prepared above added with efficient stirring. After the ad-

dition was complete, the contents were stirred at room temperature for 2 hr. and then refluxed for 6 hr. The unreacted PhLi was decomposed with H_2O and saturated NH_4Cl solution and extracted with ether. The ether layer was dried (anhy. MgSO_4) and evaporated to yield the title compound (4.92 g.; 69%) which formed a hydrochloride m.p. $204.5\text{--}205.5^\circ$ from acetone (Smisson and Hite 1959 reported m.p. $208\text{--}209^\circ$).

N-METHYL-4-BENZOYLPIPERIDINE (165)

Li sand (prepared from 2.59 g.; 0.37 mole Li metal) was suspended in ether (100 ml.) and a solution of bromobenzene (29.045 g.; 0.185 mole) in dry ether (100 ml.) was added dropwise with stirring and then refluxed for 6 hr. These contents were cooled to room temperature and N-methylisonipecotic acid hydrochloride (8.59 g.; 0.05 mole) suspended in ether was added with vigorous stirring. After the complete addition the mixture was refluxed and stirred for an additional 12 hr. The unreacted PhLi was decomposed with H_2O (40 ml.) and saturated NH_4Cl solution. The ether layer was separated, dried (anhy. MgSO_4) and evaporated. The residue was distilled under reduced pressure to yield the title compound (8.10 g.; 80%) b.p. $143\text{--}147^\circ/1.75$ mm. (Smisson and Hite 1959 reported b.p. $122^\circ/0.5$ mm.).

It formed a hydrochloride from ether which on

recrystallization from acetone melted at 203-204°
(Smismman and Hite 1959 reported m.p. 208-209°).

N-METHYL-4-CHLORO-4-PIPERIDINOPHENYL KETONE (166) HYDRO-
CHLORIDE

The title compound m.p. 177-178° was prepared according to Smismman and Hite (1959) procedure.

REARRANGEMENT OF N-METHYL-4-CHLORO-4-PIPERIDINOPHENYL
KETONE (166)

A solution of N-methyl-4-chloro-4-piperidino-phenyl ketone (4.02 g.; 0.017 mole) in xylene (50 ml.) was adding dropwise with stirring to a refluxing mixture containing xylene (200 ml.) and finely powdered and dried NaOH (18.00 g.; 0.45 mole) over a 30 min. period. The mixture was refluxed for an additional 10 min., cooled and extracted 20 times with H₂O (25 ml. portions).

The organic layer was extracted with 10% HCl solution. The aqueous layer was basified and extracted with CHCl₃. The CHCl₃ layer was dried (anhy. Na₂SO₄) and evaporated to yield N-methyl-4-hydroxyl-4-piperidinophenyl ketone (154) (1.42 g.; 41%) which on recrystallization from acetone melted at 132-135° (Smismman and Hite 1959 reported m.p. 134-135°). It formed a hydrochloride m.p. 173.5-174.5° from acetone).

ph of the aqueous phase was adjusted to about 8 with dil.HCl solution. The aqueous phase was concen-

trated to about 50 ml. and pH adjusted to about 6.5 and kept over night at room temperature. The separated solid was filtered, washed with H_2O (15 ml.), acetone (15 ml.) and ether (15 ml.). The residue (0.48 g.; 3.0%) melted at 297° (Smisson and Hite 1959 reported m.p. $309-310^{\circ}$). It formed a hydrochloride in acetone m.p. $217-219^{\circ}$ (Smisson and Hite 1959 reported m.p. $225-227^{\circ}$).

REARRANGEMENT OF N-METHYL-4-CHLORO-4-PIPERIDINOPHENYL KETONE (166)

A mixture of N-methyl-4-chloro-4-piperidino-phenyl ketone (3.19 g.; 0.014 mole), $AgNO_3$ (2.70 g.; 0.016 mole) and t-BuOH (100 ml.) was heated under reflux for 12 hr. The cooled mixture was filtered and the solvent removed from the filtrate. The residue was taken up in sat. Na_2CO_3 solution (80 ml.) and extracted with ether. The ether layer was dried (anhy. Na_2SO_4) and evaporated. The residue (1.80 g.; 62%) formed a hydrochloride m.p. 170° from acetone (previously found m.p. $173.5-174.5^{\circ}$).

The aqueous portion was neutralized carefully with dil.HCl solution. The volume was reduced to about 40 ml. and filtered. The residue dissolved in H_2O .

N-METHYL-4-PIPERIDINO-p-TOLYL KETONE (167)

A solution of p-bromotoluene (63.27 g.; 0.37 mole)

in ether (150 ml.) was added with stirring to Li sand (5.18 g.; 0.74 mole) suspended in ether (150 ml.) and refluxed for 9 hr. The cooled mixture was added to a suspension of N-methylisonipecotic acid hydrochloride (17.90 g.; 0.10 mole) in ether (150 ml.) with stirring and the contents refluxed for 20 hr. The cooled mixture was decomposed with H_2O (80 ml.) and sat. NH_4Cl solution. The ether layer was separated and the aqueous layer extracted thrice with ether. The combined ether portion was dried (anhy. MgSO_4) and evaporated. The residue was a mixture of solid and liquid.

The solid portion was separated and on recrystallization from acetone yielded N-methyl-4-piperidinodi-p-tolyl carbinol (168) (3.40 g.; 12%) m.p. $191-192^\circ$.

IR spectrum (nujol-mull):-

✓ max. 3215 (OH str.), 1600 (benzene ring) cm^{-1} .

Ana. calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}$ C, 81.55; H, 8.74.

Found: C, 81.24; H, 8.45.

The liquid portion formed a hydrochloride which on recrystallization from acetone provided the title compound (167) hydrochloride (13.83 g.; 55%) m.p. $222.5-223.5^\circ$.

IR spectrum (nujol-mull):-

✓ max. 2700-2200 (N-H^+), 1670 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{19}\text{NO.HCl}$ C, 66.27; H, 7.95.

Found: C, 66.12; H, 7.85.

N-METHYL-4-CHLORO-4-PIPERIDINO-p-TOLYL KETONE (169)

HYDROCHLORIDE

Chlorine gas was slowly bubbled into a solution of N-methyl-4-piperidino-p-tolyl ketone hydrochloride (10.30; 0.04 mole) in glacial AcOH (150 ml.) at 70° for 4 hr. with stirring. The mixture was concentrated to approximately 20 ml. and solid precipitated by adding ether (300 ml.). The residue (9.54 g.; 83%) on recrystallization from CHCl_3 provided a monohydrate of the title compound; m.p. 164-164.5°.

IR spectrum (nujol-mull):-

ν_{max} 3600-3400 (OH str.), 2760-2200 (NH^+), 1680 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{18}\text{NO} \cdot \text{HCl} \cdot \text{H}_2\text{O}$, 54.90; H, 6.86; N, 4.57.

Found: C, 54.84; H, 6.45; N, 4.65.

REARRANGEMENT OF N-METHYL-4-CHLORO-4-PIPERIDINO-p-TOLYL-KETONE (169)

A solution of N-methyl-4-chloro-4-piperidino-p-tolyl ketone (6.32 g.; 0.015 mole) in xylene (75 ml.) was added to a refluxing mixture of xylene (200 ml.) and finely powdered and dried NaOH (18.00 g.; 0.45 mole) with shaking over a 30 min. period. The mixture was refluxed for an additional 10 min. The cooled mixture was extracted 20 times with H_2O (25 ml.

each) and extracted the aqueous portion twice with ether (75 ml. each). The xylene and the ether layer were combined and extracted with 10% HCl solution. This aqueous extract was basified with 10% NaOH solution and extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. Na_2SO_4) and evaporated. The residue (3.18 g.; 53%) on recrystallization from acetone provided N-methyl-4-hydroxy-4-piperidino-p-tolyl ketone (171) with 1/2 mole of H_2O .

IR spectrum (nujol-mull):-

ν_{max} . 3200-3050 (O-H str.), 1665 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot 1/2 \text{H}_2\text{O}$ C, 69.42; H, 8.26; N, 5.79.

Found: C, 69.48; H, 7.92; N, 6.24.

This material formed a hydrochloride m.p. 201-205° from acetone.

Anal. calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2 \cdot \text{HCl} \cdot 1/2 \text{H}_2\text{O}$ C, 60.43; H, 7.55.

Found: C, 60.09; H, 7.20.

pH of the aqueous phase was adjusted to 8 with dil HCl solution and the mixture concentrated and pH adjusted to about 6.5. The residue on filtration weighed only 162 mg. and was not further purified.

N-METHYL-4-PIPERIDINO-2-THIENYL KETONE (172)

A solution of bromobenzene (29.04 g.; 0.18 mole) in ether (200 ml.) was added to a stirred suspension of Li sand (2.59 g.; 0.37 mole) in ether (200 ml.)

and the contents refluxed for 6 hr. Thiophene (16.80 g.; 0.20 mole) in ether (150 ml.) was added dropwise to the above cooled mixture with stirring and the contents refluxed again for 10 hr. The cooled mixture was then added dropwise to N-methyl-isonipecotic acid hydrochloride (8.95 g.; 0.05 mole) in ether with stirring and the entire mixture refluxed for 12 hr. The cooled mixture was decomposed with H_2O (60 ml.) and sat. NH_4Cl solution (40 ml.). The ether layer was separated and the aqueous layer extracted thrice with ether. The combined ether layer was dried (anhy. Na_2SO_4) and evaporated. The residue (8.04 g.; 80%) formed a hydrochloride which on recrystallization from ethanol yielded N-methyl-4-piperidino-2-thienyl ketone hydrochloride monohydrate, m.p. 195° .

IR spectrum (nujol-mull):-

$\sqrt{\text{max.}}$ 3500-3100 (OH str.); 2800-2200 (NH^+) 1640 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{11}\text{H}_{15}\text{NO} \cdot \text{HCl} \cdot \text{H}_2\text{O}$ C, 50.18; H, 6.84.

Found: C, 50.17; H, 6.85.

N-METHYL-4-PIPERIDINO-2-FURYL KETONE (173)

A solution of bromobenzene (29.04 g.; 0.18 mole) in ether (100 ml.) was added with stirring to a suspension of Li sand (2.59 g.; 0.37 mole) in ether (100 ml.) and the mixture refluxed for 6 hr. Furan (13.60 g.; 0.20 mole) in ether (100 ml.) was added dropwise with stirring

to the above mixture and the contents refluxed for 12 hr. The cooled mixture was added to N-methyl isonipecotic acid hydrochloride (8.95 g.; 0.05 mole) in ether (200 ml.) and the contents refluxed for 7 hr. The cooled reaction mixture was decomposed with H_2O (40 ml.) and sat. NH_4Cl solution (40 ml.). The ether layer was separated and the aqueous layer extracted twice with ether. The combined ether layer was dried (anhy. MgSO_4) and evaporated. The residue (6.51 g.; 80%) formed hydrochloride which on recrystallization from acetone provided hydrochloride of the title compound, m.p. $247.5-248^\circ$.

IR spectrum (nujol-mull):-

\checkmark max 2780-2220 $\overset{+}{\text{NH}}$, 1650 ($\text{C}=\text{O}$ str.) cm^{-1} .

Anal. calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_2\cdot\text{HCl}$ C, 57.64; H, 6.99; N, 6.02.

Found: C, 57.44; H, 6.82; N, 5.61.

ATTEMPTED PREPARATION OF N-METHYL-4-CHLORO-4-PIPERIDINO-2-THIENYL KETONE HYDROCHLORIDE

Chlorine gas was slowly bubbled into a solution of N-methyl-4-piperidino-2-thienyl ketone hydrochloride (3.04 g.; 0.012 mole) in glacial acetic acid (100 ml.) for 20 mins. The mixture was concentrated to about 15 ml. and ether (200 ml.) added. A sticky solid separated and all attempts to convert it into a crystalline solid failed.

IR spectrum (nujol-mull):-

\checkmark max. 2750-2200 $\overset{+}{\text{NH}}$, 1700 ($\text{C}=\text{O}$ str.), 1640 ($\text{C}=\text{O}$)

str.) cm^{-1} .

ATTEMPTED PREPARATION OF N-METHYL-4-BROMO-4-PIPERIDINO-2-THIENYL KETONE HYDROCHLORIDE

Bromine (1.20 g.; 0.008 mole) in dry CHCl_3 (50 ml.) was added to N-methyl-4-piperidino-2-thienyl ketone hydrochloride (1.66 g.; 0.007 mole) in dry CHCl_3 (50 ml.) dropwise with stirring at room temperature. After complete addition, the mixture was allowed to stand at room temperature over night and then filtered. The residue (1.46 g.) was dissolved in ethanol and filtered. The residue did not melt up to 300° . The residue obtained on removing the ethanol provided the starting material which had identical IR spectrum (nujol-mull) with that of the authentic sample prepared previously.

N-METHYL-4-HYDROXY-4-PIPERIDINONITRILE (182)

The title compound m.p. $137-138.5^\circ$ was prepared in 83% yield by a modified procedure of Lyle and Lyle (1954). The procedure was essentially the same except that the reaction product was extracted continuously with ether using a liquid-liquid extractor instead of the reported simple extraction with ether.

The title compound formed a methiodide m.p. 215.5° from ethanol.

Anal. calcd. for $\text{C}_7\text{H}_{12}\text{N}_2\text{O} \cdot \text{MeI}$ C, 34.04; H, 5.32.

Found: C, 33.92; H, 5.41.

N-METHYL-4-HYDROXY-4-PIPERIDINONITRILE (182)

A mixture of N-methyl-4-piperidone (22.60 g.; 0.20 mole) and acetone cyanohydrin (21.25 g.; 0.25 mole) was allowed to stand at room temperature for 10 hr. The mixture was washed with petroleum-ether and the residue (27.00 g.; 96%) on recrystallization from ethyl acetate melted at 136-140° (authentic sample m.p. 137-138.5°). IR spectrum (nujol-mull) was identical with the authentic sample of the title compound.

ATTEMPTED PREPARATION OF ETHYL-N-METHYL-4-HYDROXY-4-PIPERIDINOCARBOXYLATE (183)

A mixture of N-methyl-4-hydroxy-4-piperidino-nitrile (7.00 g.; 0.05 mole), abs. EtOH (80 ml.), conc. H_2SO_4 (8 ml.) and benzene (150 ml.) was refluxed for 8 hr. The cooled mixture was neutralized with moist Na_2CO_3 and extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. Na_2SO_4) and evaporated. The residue (5.22 g.) on recrystallization from acetone melted at 136-138° (melting point of the starting material 137-138.5°). IR spectrum (nujol-mull) was identical with that of the starting material.

ETHYL-N-METHYL-4-HYDROXY-4-PIPERIDINOCARBOXYLATE (183)

The title compound b.p. 93-94°/1.1 mm. was prepared according to the procedure of Lyle and Lyle (1954).

IR spectrum (film):-

\checkmark max. 3500-3100 (OH str.); 1700 (C=O str.) cm^{-1} .

N-METHYL-4-HYDROXY-4-PIPERIDINODIPHENYLCARBINOL (184)

The title compound m.p. 155-156.5° was prepared according to the procedure of Lyle and Lyle (1954). It formed a hydrochloride monohydrate m.p. 158-160° from ethanol (Lyle and Lyle 1954 reported m.p. 207-208° for the hydrochloride).

IR spectrum (nujol-mull):-

\checkmark max. 3500-3100 (OH str.), 2740-2200 (NH⁺) cm^{-1} .

Carbonyl band (1700 cm^{-1}) disappeared.

Anal. calcd. for $\text{C}_{19}\text{H}_{23}\text{NO}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$ C, 64.85; H, 7.44; N, 3.93.

Found: C, 65.56; H, 7.62; N, 3.97.

N-METHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE (185)

The title compound m.p. 77.5-78.5° was prepared according to the procedure of Lyle and Lyle (1954) in about 87% yield.

IR spectrum (nujol-mull):-

\checkmark max. 1670 (C=O str.) cm^{-1} . Hydroxyl bands (3500-3200 cm^{-1}) present in the starting material disappeared.

OXIMATION OF N-METHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE

A mixture of N-methyl-4-phenyl-4-piperidinophenyl ketone (2.43 g.; 0.0087 mole), hydroxylamine hydro-

chloride (0.76 g.; 0.0096 mole), pyridine (4 ml.) and ethanol (5 ml.) was heated on the steam bath for 3 hr. to dissolve all the reactants. The solvents were removed and the residue (1.30 g.; 50%) on recrystallization from abs. EtOH afforded the oxime (177) hydrochloride, m.p. 267° . It gave a positive AgNO_3 test.

IR spectrum (nujol-mull):-

\nearrow max. 3180 (OH str.), $2750-2200$ (NH) cm^{-1} .

Carbonyl band (1670 cm^{-1}) disappeared.

Anal. calcd. for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O} \cdot \text{HCl}$ C, 68.97; H, 7.01.

Found: C, 68.61; H, 6.93.

ATTEMPTED SYNTHESIS OF N-METHYL-4-PHENYL-4-PIPERIDINO-CARBOXYLIC ACID (153) HYDROCHLORIDE

Dry hydrogen chloride gas was passed through a suspension of oxime of N-methyl-4-phenyl-4-piperidino-phenyl ketone hydrochloride (1.00 g.; 0.003 mole) in glacial AcOH (100 ml.). After a few minutes, complete solution occurred. The whole mixture was then heated on a steam bath while hydrogen chloride gas was slowly bubbled in for 2 hr. The AcOH was removed by distillation under reduced pressure and the residue on recrystallization from ethanol provided the starting material (400 mg.) m.p. $261-262^{\circ}$. IR spectrum (nujol-mull) was also identical with that of the starting material.

ATTEMPTED PREPARATION OF N-METHYL-4-CHLORO-4-PIPERI-
DINONITRILE (187)

A solution of thionyl chloride (11.80 g.; 0.10 mole) in CHCl_3 (100 ml.) was added with stirring to a solution of N-methyl-4-hydroxy-4-piperidinonitrile (7.00 g.; 0.05 mole) in CHCl_3 (150 ml.). After the complete addition, the mixture was stirred for an additional 6 hr. and then allowed to stand at room temperature over night. The solvent and the unreacted thionyl chloride were then removed and the residue (9.25 g.) on recrystallization from abs. ethanol provided the hydrochloride of the starting material, m.p. $180-181^\circ$ (mixed melting point with the authentic sample $182-183^\circ$). IR spectrum (nujol-mull) was identical with that of the hydrochloride of the starting material.

ATTEMPTED SYNTHESIS OF N-METHYL-4-CHLORO-4-PIPERIDI-
NONITRILE (187) HYDROCHLORIDE

Thionyl chloride (10 ml.) was added dropwise with shaking to N-methyl-4-hydroxy-4-piperidinonitrile hydrochloride (2.00 g.; 0.013 mole). The mixture was allowed to stand at room temperature over night and then refluxed for 8 hr. The excess thionyl chloride was removed and the residue on recrystallization from ethanol provided N-methyl-4-cyano-1,2,5,6-tetrahydropyridine (188) hydrochloride m.p. $175-176$.

IR spectrum (nujol-mull):-

✓ max. 2750-2220 (NH)⁺, 2200 (C≡N str.) cm^{-1} . Hydroxyl band (3500-3200 cm^{-1}) disappeared.

PMR spectrum (D_2O):-

181 Hz (N-methyl singlet), 408 Hz (=CH), 250-160 Hz (various peaks; six piperidine ring protons).

Anal. calcd. for $\text{C}_7\text{H}_{10}\text{N}_2\cdot\text{HCl}$ C, 53.00; H, 6.99.

Found: C, 52.99; H, 7.00.

N-METHYL-4-ACETOXY-4-PIPERIDINONITRILE (191) HYDROCHLORIDE

A mixture of N-methyl-4-hydroxy-4-piperidinonitrile (2.80 g.; 0.02 mole), pyridine (3 ml.) and Ac_2O (6 ml.) was refluxed for 3 hr. and the unreacted Ac_2O and pyridine removed by distillation under reduced pressure. The residue was taken up in ether, shaken well and filtered and the solvent removed from the filtrate. The residue formed a hydrochloride m.p. 191-192° from acetone.

IR spectrum (nujol-mull):-

✓ max. 2740-2100 (NH), 1755 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2\cdot\text{HCl}$ C, 49.43; H, 6.91.

Found: C, 49.18; H, 7.18.

N-PHENETHYL-4-HYDROXY-4-PIPERIDINONITRILE (190)

A mixture of N-phenethyl-4-piperidone (5.08 g.; 0.025 mole), and acetone cyanohydrin (4.25 g.; 0.05 mole) was shaken well and allowed to stand at room temperature for 6 hr. At the end of this time, the reaction mixture solidified. The reaction product was separated by filtration and on recrystallization from benzene-petroleum ether melted at 89-91°. Yield 5.03 g.; 80% (Harper and Fullerton 1961, reported m.p. 93°).

N-PHENETHYL-4-ACETOXY-4-PIPERIDINONITRILE (191)

N-Phenethyl-4-acetoxy-4-piperidinonitrile was pre-

pared by pyridine method from the corresponding cyano-hydrin according to the procedure of Harper and Fullerton (1961). It formed a hydrochloride m.p. $257-258^{\circ}$ from acetone (Harper and Fullerton 1961 reported m.p. 258.5°).

IR spectrum (nujol-mull):-

ν_{\max}^{C} . 2700-2200 (NH^+), 1760 (C=O str.) cm^{-1} .

1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINONITRILE (192)

The title compound, m.p. $87-90^{\circ}$ was prepared according to the procedure of Unkovskii, et. al. (1961).

1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINONITRILE (192)

1,3-Dimethyl-4-piperidone (12.70 g.; 0.10 mole) was added to a cold saturated solution of KCN (7.20 g.; 0.11 mole) in H_2O (15 ml.) with stirring in about 15 min. Dil.HCl solution was added to the above mixture with cooling until the solution was slightly acidic. The mixture was neutralized with K_2CO_3 and excess K_2CO_3 (5.00 g.) added to salt out the cyanohydrin. The basic material was extracted with ether and the ether removed without drying. The residue on recrystallization from ethyl acetate provided the title compound (10.30 g.; 66%) m.p. $89-91^{\circ}$ (Unkovskii et. al. 1961, reported m.p. $88-90^{\circ}$).

This compound (192) formed a hydrochloride m.p. $158-159^{\circ}$ from ethanol.

IR spectrum (nujol-mull):-

✓max. 3170 (OH str.), 2760-2200 (NH) cm^{-1} .

Anal. calcd. for $\text{C}_8\text{H}_{14}\text{N}_2\text{O} \cdot \text{HCl}$ C, 50.39; H, 7.87.

Found: C, 50.49; H, 7.68.

1,3-DIMETHYL-4-ACETOXY-4-PIPERIDINONITRILE (193)

A mixture of 1,3-dimethyl-4-hydroxy-4-piperidino-nitrile (3.08 g.; 0.02 mole), pyridine (3 ml.) and Ac_2O (6 ml.) was heated at 120° for 3 hr. The unreacted Ac_2O and pyridine were then removed. The residue was taken up in ether, and filtered. The removal of ether from the filtrate by evaporation provided the title compound (4.10 g.) in quantitative yield.

This compound (193) formed a hydrochloride, m.p. $234.5-235^\circ$.

IR spectrum (nujol-mull):-

✓max. 2750-2200 (NH), 1755 (C=O str.) cm^{-1} .

Anal. calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2 \cdot \text{HCl}$ C, 51.50; H, 7.29.

Found: C, 51.31; H, 7.32.

1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINOCARBOXYLIC ACID

(204) HYDROCHLORIDE

The title compound m.p. $192-193^\circ$ was prepared according to the procedure of Unkovskii et. al. 1961.

IR spectrum (nujol-mull):-

✓max. 3400 (OH str.), 2760-2200 (NH), 1720 (C=O str.) cm^{-1} .

ETHYL 1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINOCARBOXYLATE

(205)

A mixture of 1,3-dimethyl-4-hydroxy-4-piperidino-carboxylic acid hydrochloride (12.80 g.; 0.06 mole), conc. H_2SO_4 (16 ml.) and abs. EtOH (150 ml.) was refluxed for 16 hr. A portion of the solvent (100 ml.) was then removed, the residue basified with NH_4OH solution and the reaction product extracted with CHCl_3 . The CHCl_3 layer was dried (anhy. K_2CO_3) and evaporated. The residue on distillation under reduced pressure provided the title compound (6.80 g.; 55%) b.p. $106^\circ/3$ mm. (Unkovskii et. al. 1961 reported b.p. $99-101^\circ/1.5$ mm.).

This compound (205) formed a hydrochloride m.p. $157.5-158.5^\circ$ from acetone (Unkovskii et. al. 1961 reported m.p. $148-150^\circ$).

IR spectrum (nujol-mull):-

\checkmark max. 3260 (OH str.), $2770-2240$ (NH), 1732 (C=O str.) cm^{-1} .

1,3-DIMETHYL-4-HYDROXY-4-PIPERIDINODIPHENYLCARBINOL

(206) HYDROCHLORIDE

A solution of bromobenzene (17.58 g.; 0.11 mole) in ether (150 ml.) was added dropwise to a stirred suspension of Li sand (1.57 g.; 0.22 mole) in ether (100 ml.) and the mixture refluxed for 12 hr. A solution of ethyl 1,3-dimethyl-4-hydroxy-4-piperidinocarboxylate (5.80 g.; 0.028 mole) in ether (150 ml.) was

added to the above cooled mixture with stirring and the entire reaction mixture refluxed for 6 hr. The cooled mixture was poured into ice with shaking and the reaction product was extracted with 20% HCl solution. The solid separated on allowing the aqueous extract to stand at room temperature for about 1/2 hr. was separated by filtration and the residue freed from traces of H_2O by azeotropic distillation with benzene. The residue on recrystallization from acetone afforded the title compound (7.92 g.; 82%) m.p. 258-259° (Unkovskii et. al. 1961 reported m.p. 259-259.5°).

1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE (202)

The title compound (202) m.p. 115-117° was obtained in 82% yield using the procedure of Unkovskii et. al. (1961).

IR spectrum (nujol-mull):-

$\nu_{\text{max.}}$ 1675 (C=O str.) cm^{-1} .

This material formed a hydrochloride m.p. 275-275.5° from EtOH.

IR spectrum (nujol-mull):-

$\nu_{\text{max.}}$ 2770-2200 $^{+}$ (NH), 1700 (C=O str.) cm^{-1} .

Anal. calcd. for $C_{20}H_{23}NO.HCl$ C, 72.94; H, 7.29; N, 4.25.

Found: C, 72.32; H, 7.49; N, 4.25.

~~X~~-1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE
(220)

Bromobenzene (10.90 g.; 0.10 mole) in ether (100

ml.) was added dropwise to a stirred suspension of magnesium turnings (18.30 g.; 0.075 mole) in ether (100 ml.) and a crystal of iodine and the mixture was refluxed for 10 hr. To the cooled mixture, ~~X~~ -1,3-dimethyl-4-phenyl-4-piperidinonitrile (5.38 g.; 0.025 mole) in toluene (100 ml. was added dropwise with stirring. After the complete solution, the ether was distilled off and the remainder refluxed for 10 hr. The cooled mixture was hydrolyzed with dil. HCl solution, the aqueous portion separated and the toluene layer extracted with dil. HCl solution. The combined aqueous portion was basified with NaOH (solid) and the reaction product extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (6.12 g.) was a liquid.

IR spectrum (film):-

✓ max. 1675 (C=O str.) cm^{-1} . Nitrile band ($2220\ cm^{-1}$) present in the starting material disappeared.

This material formed a hydrochloride m.p. 231-235° from acetone.

IR spectrum (nujol-mull):-

✓ max. 3600-3100 (OH str.), 2800-2200 (NH), 1695⁺ (C=O str.) cm^{-1} .

Anal. calcd. for $C_{20}H_{23}NO.HCl$ C, 69.16; H, 7.44.

Found: C, 69.33; H, 7.34.

β -1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE
(219)

Bromobenzene (9.42 g.; 0.06 mole) in ether (100 ml.) was added dropwise to a stirred suspension of Li sand (0.84 g.; 0.12 mole) in ether (100 ml.) After the addition was complete, the mixture was re-fluxed for 12 hr. β -1,3-Dimethyl-4-phenyl-4-piperidinonitrile (4.90 g.; 0.023 mole) in ether (100 ml.) was added to the cooled reaction mixture with stirring and the contents refluxed for 12 hr. The cooled mixture was decomposed with H_2O and the reaction product extracted with 10% HCl solution (100 ml.). The aqueous portion was basified with KOH (solid) and extracted with ether. The ether layer was dried (anhy. K_2CO_3) and evaporated. The residue (6.30 g.; 96%) on recrystallization from ligroin yielded β -1,3-dimethyl-4-phenyl-4-piperidinophenyl ketimine (221), m.p. 116-118°.

IR spectrum (nujol-mull):-

ν_{max} . 3140 (N-H str.), 1620 (C=N str.) cm^{-1} .

Anal. calcd. for $C_{20}H_{24}N_2$ N, 9.59.

Found: N, 9.81.

This ketimine (221) formed a dihydrochloride in ether which on recrystallization from ethanol melted at 262.5-264.5°.

IR spectrum (nujol-mull):-

ν_{max} . 3500-3200 (N-H str.), 2750-2200 ($N-H^+$), 1665

(C=N-H)⁺ cm⁻¹.

Anal. calcd. for C₂₀H₂₄N₂.2HCl N, 7.67.

Found: N, 7.36.

The ketimine (221) was heated with 10% HCl solution for 12 hr. The cooled mixture was basified with 40% NaOH solution and extracted with ether. The ether layer was dried (anhy. K₂CO₃) and evaporated. The residue on recrystallization from ligroin afforded the title compound (219), m.p. 115-117°. IR spectrum (nujol-mull) of this ketone was identical with that of the ketone obtained by ZnCl₂-Ac₂O rearrangement of the diol (206).

This ketone formed a hydrochloride (m.p. 274-275° from ether. No depression in melting point was noticed when mixed m.p. of this hydrochloride was determined with the authentic sample prepared previously by rearrangement route. IR spectrum (nujol-mull) was also identical with that of the ketone hydrochloride obtained previously.

ATTEMPTED OXIMATION OF 1,3-DIMETHYL-4-PHENYL-4-PIPERIDINOPHENYL KETONE (219)

A mixture of 1,3-dimethyl-4-phenyl-4-piperidinophenyl ketone (2.93 g.; 0.01 mole), pyridine (4 ml.), hydroxylamine hydrochloride (0.94 g.; 0.011 mole) and abs. ethanol (5 ml.) was heated on a steam bath for 3 hr. and the solvents removed. The residue on

recrystallization from abs. EtOH provided the hydrochloride of the starting material (m.p. and mixed m.p. 275-275.5°). IR spectrum (nujol-mull) of this product was identical with that of the authentic sample of the ketone (219) hydrochloride.

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